



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 14/655, C07D 33/64, A61K 31/4164, 38/31	A1	(11) International Publication Number: WO 99/65942 (43) International Publication Date: 23 December 1999 (23.12.99)
(21) International Application Number: PCT/US99/13304 (22) International Filing Date: 11 June 1999 (11.06.99) (30) Priority Data: 09/098,181 16 June 1998 (16.06.98) US 60/089,503 16 June 1998 (16.06.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 09/098,181 (CON) Filed on 16 June 1998 (16.06.98) US 60/089,503 (CON) Filed on 16 June 1998 (16.06.98) (71) Applicant (for all designated States except US): SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A. [FR/FR]; 51-53, rue du Docteur Blanche, F-75016 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): GORDON, Thomas, D. [US/US]; 6 Rainbow Drive, Medway, MA 02053 (US).		(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CYCLIC SOMATOSTATIN ANALOGS (57) Abstract <p>The present invention is directed to cyclic derivatives containing an imidazole <i>cis</i> amide bond mimetic which bind selectively to somatostatin receptor subtypes and the use thereof in treating conditions which can be treated by eliciting an agonist or antagonist effect from the somatostatin subtype receptors. This invention is also directed to methods for making the compounds of the instant invention.</p>		

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CYCLIC SOMATOSTATIN ANALOGS

Background Of The Invention

5 The present invention is directed to cyclic derivatives containing an imidazole *cis* amide bond mimetic which bind selectively to somatostatin receptor subtypes. This invention is also directed to methods for making the compounds of the instant invention.

 Somatostatin (SRIF) is a cyclic tetradecapeptide hormone containing a
10 disulfide bridge between position 3 and position 14 and has the properties of inhibiting the release of growth hormone (GH) and thyroid-stimulating hormone (TSH), inhibiting the release of insulin and glucagon, and reducing gastric secretion. Metabolism of somatostatin by aminopeptidases and carboxypeptidases leads to a short duration of action.

15 Somatostatin binds to five distinct receptor (SSTR) subtypes with relatively high affinity for each subtype. The smaller, more rigid analogs of the present invention exhibit high selectivity for several of the receptor subtypes. Binding to the different types of somatostatin subtypes have been associated with the treatment of the following conditions and/or diseases. Activation of types 2 and 5 have been
20 associated with growth hormone suppression and more particularly GH secreting adenomas (Acromegaly) and TSH secreting adenomas. Activation of type 2 but not type 5 has been associated with treating prolactin secreting adenomas. Other indications associated with activation of the somatostatin subtypes are restenosis, inhibition of insulin and/or glucagon and more particularly diabetes mellitus,
25 hyperlipidemia, insulin insensitivity, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon and Nephropathy; inhibition of gastric acid secretion and more particularly peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery diarrhea syndrome, AIDS related diarrhea, chemotherapy-induced diarrhea, acute or chronic pancreatitis
30 and gastrointestinal hormone secreting tumors; treatment of cancer such as hepatoma; inhibition of angiogenesis, treatment of inflammatory disorders such as arthritis; chronic allograft rejection; angioplasty; preventing graft vessel and

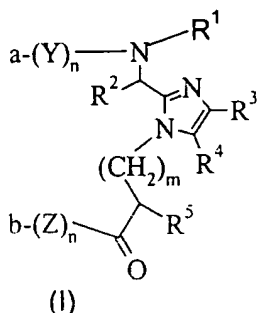
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gastrointestinal bleeding. Somatostatin agonists can also be used for decreasing body weight in a patient.

Somatostatin agonists have also been disclosed to be useful for inhibiting the proliferation of *helicobacter pylori*.

Summary Of The Invention

In one aspect, the present invention provides a compound of the formula (I),



or a pharmaceutically acceptable salt thereof,

wherein,

- 10 Y and Z for each occurrence are each independently a D- or L-natural or unnatural α -amino acid;
- n for each occurrence is independently 0 to 50, provided that both n cannot be 0 at the same time;
- m is 0 or an integer from 1 to 10;
- 15 a is H or R¹;
- b is OH, -OR¹ or -NR⁹R⁹;
- or a is taken together with b to form an amide bond;
- R¹ is independently H, (C₁-C₄)alkyl or aryl-(C₁-C₄)alkyl;
- R² is H or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl, phenyl, phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the
- 20 optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, -O-R⁶, -S(O)_q-R⁷, -N(R⁹R⁹), -NHCO-R⁶, -NHSO₂R⁹, -CO₂R⁹, -CONR⁹R⁹ and -SO₂NR⁹R⁹, where q is 0,
- 25 1, 2 or 3;

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R³ and R⁴ are each independently H, halo or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl and aryl-(C₁-C₄)alkyl; where the optionally substituted moiety is optionally substituted by one or more substituents selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;
 5 or R³ and R⁴ are taken together with the carbons to which they are attached to form optionally substituted aryl, where the aryl is optionally substituted by one or more substituents each independently selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOR⁵, -CONR⁹R⁹ and
 10 halo;

R⁵ for each occurrence is independently H, or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl and aryl-(C₁-C₄)alkyl, where the optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, OH, (C₁-C₄)alkoxy, aryloxy, NO₂, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;
 15 C₄)alkoxy, aryloxy, NO₂, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;

R⁶ for each occurrence is independently selected from the group consisting of H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryl-(C₁-C₄)alkyl and aryl-(C₁-C₄)alkoxy;

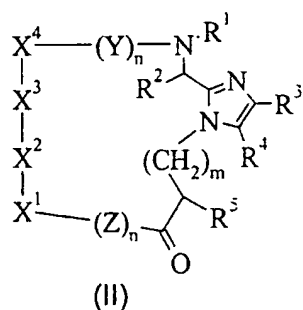
R⁷ is H when q is 3 or, R⁷ for each occurrence is independently selected from the group consisting of (C₁-C₄)alkyl, aryl or aryl-(C₁-C₄)alkyl when q is 0, 1 or
 20 2; and

R⁹ for each occurrence is independently selected from the group consisting of H, NO₂, (C₁-C₄)alkyl, aryl and aryl-(C₁-C₄)alkyl.

A preferred compound of formula (I) is the compound H-Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly-OH.

25 In another aspect, the present invention provides a compound of the formula (II),

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or a pharmaceutically acceptable salt thereof,

wherein,

Y and Z for each occurrence are each independently a D- or L-natural or unnatural
 5 α -amino acid;

m is 0 or an integer from 1 to 10;

n for each occurrence is independently 0 to 6;

R¹ for each occurrence is independently H, (C₁-C₄)alkyl or aryl-(C₁-C₄)alkyl;

R² is H or an optionally substituted moiety selected from the group consisting of (C₁-
 10 C₄)alkyl, phenyl, phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the
 optionally substituted moiety is optionally substituted by one or more substituents
 each independently selected from the group consisting of (C₁-C₄)alkyl, cycloalkyl, -O-
 R⁶,

-S(O)_q-R⁷, -N(R⁹R⁹), -NHCO-R⁶, -NHSO₂R⁹, -CO₂R⁹, -CONR⁹R⁹ and -SO₂NR⁹R⁹,

15 where q is 0, 1, 2 or 3;

R³ and R⁴ are each independently H, halo or an optionally substituted moiety
 selected from the group consisting of (C₁-C₄)alkyl, cycloalkyl, aryl and aryl-(C₁-
 C₄)alkyl; where the optionally substituted moiety is optionally substituted by one or
 more substituents selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-

20 C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;

or R³ and R⁴ are taken together with the carbons to which they are attached to form
 optionally substituted aryl, where the aryl is optionally substituted by one or more
 substituents each independently selected from the group consisting of OH, (C₁-
 C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOR⁵, -CONR⁹R⁹ and
 25 halo;

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R⁵ for each occurrence is independently H, or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl and aryl-(C₁-C₄)alkyl, where the optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, OH, (C₁-C₄)alkoxy, aryloxy, NO₂, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;

R⁶ for each occurrence is independently selected from the group consisting of H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryl-(C₁-C₄)alkyl and aryl-(C₁-C₄)alkoxy;

R⁷ is H when q is 3, or R⁷ for each occurrence is independently selected from the group consisting of (C₁-C₄)alkyl, aryl or aryl-(C₁-C₄)alkyl when q is 0, 1 or

2; and

R⁹ for each occurrence is independently selected from the group consisting of H, NO₂, (C₁-C₄)alkyl, aryl and aryl-(C₁-C₄)alkyl.

X¹ is a natural or unnatural D- or L- α -amino acid, where when X¹ is Phe, Nal, Trp,

Tyr, Pal or His the aromatic ring thereof is optionally substituted on carbon or

nitrogen by R⁶ or when X¹ is Ser or Thr, the side chain oxygen is optionally substituted by one or more R¹;

X² is D- or L-Trp, N-methyl-D-Trp or N-methyl-L-Trp;

X³ is Lys, α -N-methyl-Lys or ϵ -N-(C₁-C₄)alkyl-Lys or ϵ -N-[aryl-(C₁-C₄)alkyl]-Lys;

X⁴ is a natural or unnatural D- or L- α -amino acid where when X⁴ is Phe, Nal, Trp, Tyr

or His, the aromatic ring thereof is optionally substituted on carbon or nitrogen by R⁶ or when X⁴ is Ser, Tyr or Thr, the side chain oxygen may be substituted with one or more R¹.

The bonds between X¹, X², X³ and X⁴ are amide bonds as is the bond between X¹ and Z, and the bond between X⁴ and Y.

A preferred group of compounds of formula (II), designated group A, is wherein,

each n is 2;

m is 0 or 1 to 5;

R¹ for each occurrence is independently H, methyl or aryl-(C₁-C₄)alkyl;

R² is an optionally substituted moiety selected from the group consisting phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the optionally substituted moiety is

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substituted by a substituent selected from the group consisting of (C₁-C₄)alkyl and -O-R⁶; and

R³ and R⁴ are each independently H, halo or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl and aryl; where the optionally

- 5 substituted moiety is optionally substituted by a substituent selected from the group consisting of OH, (C₁-C₄)alkoxy, aryloxy and halo.

A preferred group of the group A compounds, designated group B, is wherein X¹ is Phe, Nal, Trp, Tyr, Pal or His, wherein the aromatic ring thereof is optionally substituted on carbon or nitrogen by R⁶; and

- 10 X⁴ is Val, Abu, Ser, Thr, Nal, Trp, Tyr or His, wherein the aromatic ring of Nal, Trp, Tyr and His is optionally substituted on carbon and/or nitrogen by R⁸ or when X⁴ is Ser, Tyr or Thr, the side chain oxygen is optionally substituted by R¹.

A preferred group of the group B compounds, designated group C, is wherein X¹ is Phe, Trp or Tyr wherein the aromatic ring thereof is optionally substituted on

- 15 carbon or nitrogen by R⁶;

X² is D-Trp or N-methyl-D-Trp;

X³ is Lys or α-N-methyl-Lys;

X⁴ is Val, Thr, Abu, Nal or Tyr, wherein the side chain oxygen of the hydroxy group of Thr and Tyr is optionally substituted by R¹;

- 20 R¹ for each occurrence is independently H, methyl or benzyl;

R² is an optionally substituted moiety selected from the group consisting phenylmethyl and heterocyclyl-methyl, where the optionally substituted moiety is substituted by a substituent selected from the group consisting of (C₁-C₄)alkyl and -O-R⁶;

- 25 R³ is (C₁-C₄)alkyl or optionally substituted aryl; where the optionally substituted aryl is substituted by a substituent selected from the group consisting of OH, (C₁-C₄)alkoxy, aryloxy, and halo;

R⁴ is H; and

R⁶ for each occurrence is independently selected from the group consisting of H and

- 30 aryl-(C₁-C₄)alkoxy.

A preferred group of the group C compounds, designated group D, is wherein

X¹ is Phe, Trp, Tyr or Tyr(OBzl);

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X⁴ is Val, Thr, Abu, Nal, or Tyr, wherein the hydroxy group of Thr and Tyr is optionally substituted benzyl;

m is 0, 2 or 4;

R² is an optionally substituted moiety selected from the group consisting of

5 phenylmethyl or 3-indolylmethyl where the optionally substituted moiety is optionally substituted by -O-R⁶; and

R³ is 1,1-dimethylethyl or optionally substituted aryl; where the optionally substituted aryl is optionally substituted by a moiety selected from the group consisting of OH, (C₁-C₄)alkoxy and halo.

10 A preferred group of the group D compounds, designated group E, is wherein R² is phenylmethyl;

R³ is 1,1-dimethylethyl or optionally substituted phenyl, where the optionally substituted phenyl is optionally substituted by OH or OCH₃; and

15 R⁶ for each occurrence is independently selected from the group consisting of H or benzylmethoxy.

A preferred group of the group E compounds, designated group F, is
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Tyr(OBzl)-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 20 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole)-Gly],
 25 cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 30 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],

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- cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],
 cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(phenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(ε)Ahx] and
 5 cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-hydroxyphenyl)imidazole-(γ)Abu].

- A preferred group of the group F compounds, designated group G, is
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Tyr(OBzl)-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 10 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole-Gly],
 15 cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly] and
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

- A preferred group of the group G compounds, designated group H, is
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 20 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly] or
 25 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

- A preferred group of the group H compounds, designated group I, is
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly] and
 30 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

Another preferred group of the group F compounds, designated group J, is

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- cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 5 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 10 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],
 15 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(ε)Ahx] and
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-hydroxyphenyl)imidazole-(γ)Abu].

A preferred group of the group J compounds, designated group K, is

- 20 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly] or
 25 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly].

A preferred group of the group K compounds, designated group L, is

- cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],
 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly] and
 30 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly].

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In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5 In still another aspect, the present invention provides a method of eliciting a somatostatin receptor agonist effect in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

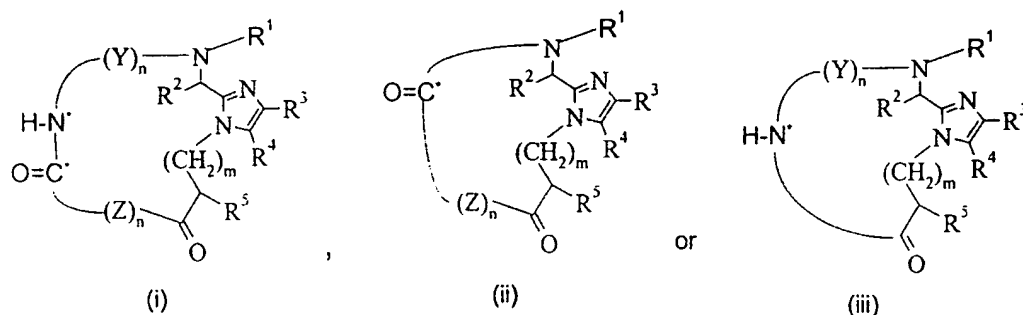
10 In yet another aspect, the present invention provides a method of eliciting a somatostatin receptor antagonist effect in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound according of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

15 In another aspect, the present invention provides a method of treating prolactin secreting adenomas restenosis, diabetes mellitus, hyperlipidemia, insulin insensitivity, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon, Nephropathy, gastric acid secretion, peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery diarrhea syndrome, AIDS related diarrhea, chemotherapy-induced diarrhea, acute or chronic pancreatitis, gastrointestinal hormone secreting tumors, cancer, hepatoma, 20 angiogenesis, inflammatory disorders, arthritis, chronic allograft rejection, angioplasty, graft vessel bleeding or gastrointestinal bleeding, in a mammal in need thereof, which comprises administering to said mammal a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

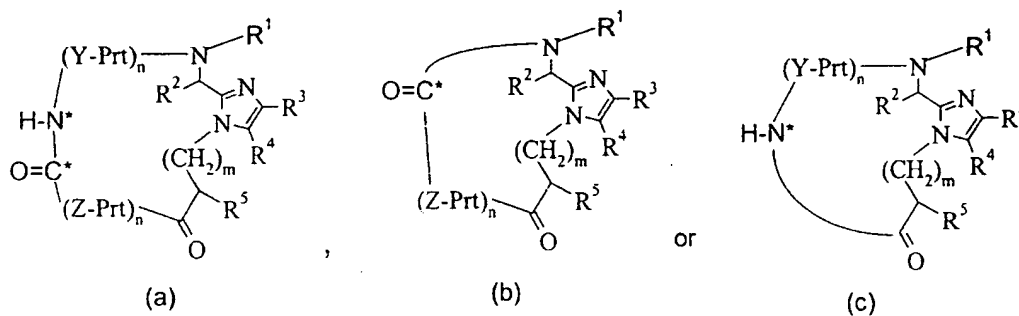
25 In another aspect, this invention provides a method of inhibiting the proliferation of *helicobacter pylori* in a mammal in need thereof, which comprises administering to said mammal a compound of formula (I) or formula (II) or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides a process for preparing a compound of the formula

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which comprises deprotecting a compound of the formula



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by cleaving the Prt group;

wherein,

Prt is an amino acid side chain protecting group;

Y and Z are each independently a D- or L-natural or unnatural α -amino acid

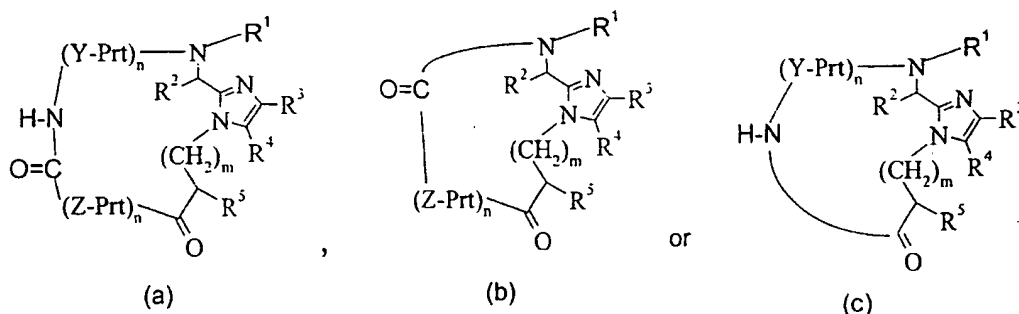
- 10 optionally having a protected side chain, where the H-N* is the amino group of the N-terminal amino acid defined by Y and O=C* is the carboxyl group of the C-terminal amino acid defined by Z;

n for each occurrence is independently 1 to 50;

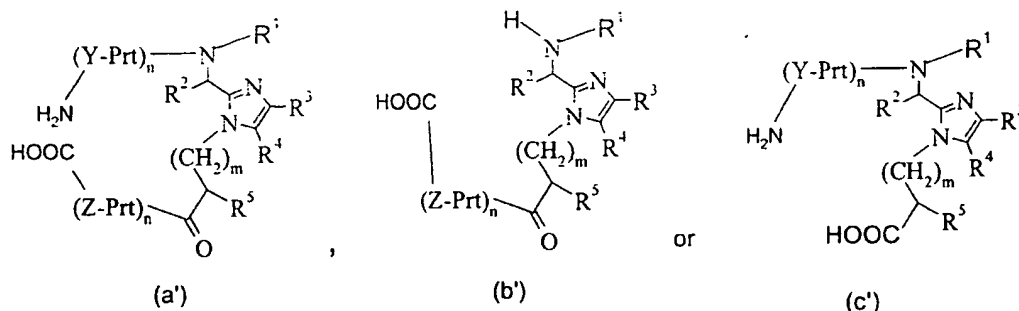
and all other variables are as defined for formula (I) shown hereinabove.

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In another aspect, the present invention provides, a process for preparing a compound of the formula



5 which comprises:



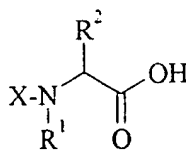
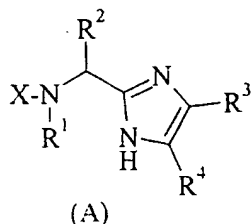
- for a compound of formula (a), forming an amide bond between the terminal amino group of the last amino acid defined by Y and the terminal carboxyl group of the last amino acid defined by Z by reacting a compound of the formula (a') with a peptide coupling reagent and an additive; or
- 10 for a compound of formula (b), forming an amide bond between the terminal amino group, and the terminal carboxyl group of the last amino acid defined by Z by reacting a compound of the formula (b') with a peptide coupling reagent and an additive; or
- 15 for a compound of formula (c), forming an amide bond between the terminal amino group of the last amino acid defined by Y and the terminal carboxyl group by reacting a compound of the formula (c') with a peptide coupling reagent and an additive;
- wherein, Prt is an amino acid side chain protecting group;
- 20 Y and Z are each independently a D- or L-natural or unnatural α -amino acid optionally having a protected side chain, where the H-N* is the amino group of the N-

terminal amino acid defined by Y and ⁻¹³⁻ O=C* is the carboxyl group of the C-terminal amino acid defined by Z;

n for each occurrence is independently 1 to 50;

and all other variables are as defined for formula (I) shown hereinabove.

- 5 In still another aspect, the present invention provides a process for preparing a compound of the formula



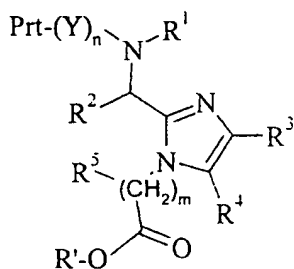
which comprises reacting a compound of the formula with an α -halo ketone of the formula $X'-CH(R^3)CO(R^4)$ in the presence of a base and a polar aprotic solvent until the reaction is substantially complete; evaporating the polar aprotic solvent to yield a solid; dissolving the solid in an aprotic organic solvent and an excess amount of aqueous NH_4OAc to form a solution; and refluxing the solution and concurrently removing that polar layer to yield a compound of formula (A); wherein

- 15 X is an amine protecting group;
X' is halo;

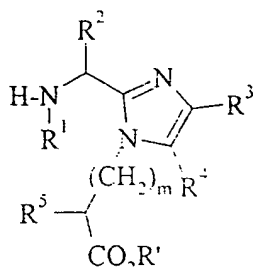
and all other variables are as defined for formula (I) shown hereinabove.

In yet another aspect, this invention provides a process for preparing a compound of the formula (I),

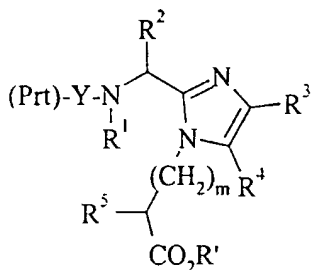
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(I) which comprises coupling a compound of the



formula (B), (B), with an N_α -protected amino acid, (Prt)-Y, where the N_α -protected amino acid is in the form of its activated ester, anhydride or acid halide, in the presence of a base until the reaction is substantially complete to yield a

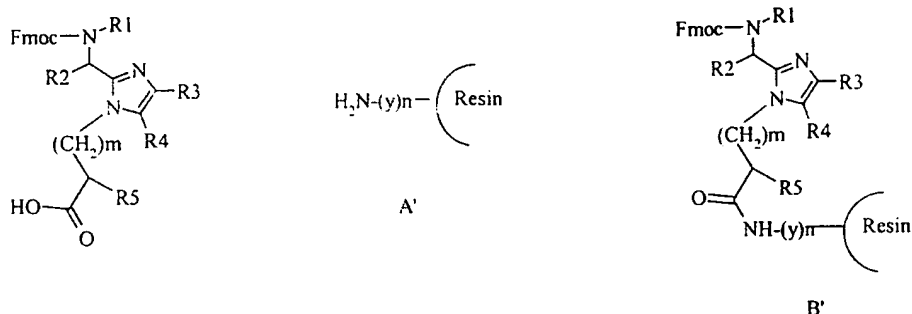


- 5 compound of the formula (C), (C), optionally deprotecting the amino group of the N_α -protected amino acid, (Prt)-Y, using a conventional deprotecting reaction and repeating the coupling reaction with another N_α -protected amino acid repeatedly until the desired compound of formula (I) is obtained; Y for each occurrence is independently a D- or L-natural or unnatural α -amino acid
- 10 optionally having a side chain with a protecting group;
- Prt is an amine protecting group;
- R' is an alkyl ester or benzyl ester;
- n is 1 to 100;

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and all other variables are as defined for formula (I) shown hereinabove.

In another aspect, this invention provides a process for preparing a compound of formula (I), as defined hereinabove, which comprises coupling a compound of formula (B), activated as it's active ester, anhydride, or acid halide, with an N-deprotected peptide-resin (A'), prepared by methods well known to those familiar with the peptide synthesis, deprotecting the N-terminal Fmoc group using piperidine in DMF, TAEA, or similar base and deprotecting and cleaving the resulting intermediate (B') from the resin using a strong acid. All variables are as defined for formula (I) shown hereinabove.



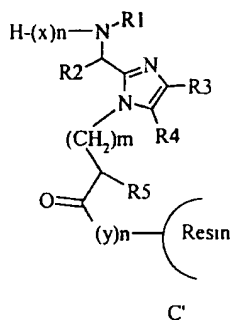
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B

In another aspect, this invention provides, a process for preparing a compound of formula (I), which comprises coupling a compound of formula (B), activated as it's active ester, anhydride, or acid halide, with an N-deprotected peptide-resin (H), prepared by methods well known to those familiar with peptide synthesis, deprotecting the N-terminal Fmoc group using piperidine in DMF, TAEA, or similar base, acylating the liberated N-terminal amino group with an N_α-Fmoc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the base deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting and cleaving the resulting intermediate (C') from the resin using a strong acid. All variables are as defined for formula (I) shown hereinabove.

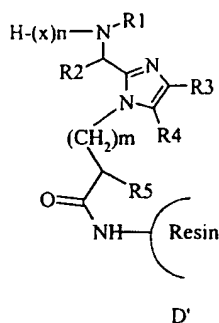
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In another aspect, this invention provides, a process for preparing a compound of formula (I), which comprises coupling a compound of formula (B), activated as it's active ester, anhydride, or acid halide, to an amino-substituted resin, such as Tris-(alkoxy)-benzylamine resin (PAL Resin), 4-(2',4'-Dimethoxyphenyl-aminomethyl)-phenoxy Resin (N-deprotected Rink resin), or Benzhydrylamine resin, deprotecting the N-terminal terminal Fmoc group using piperidine in DMF, TAEA, or similar base, acylating the liberated N-terminal amino group with an N_α-Fmoc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the base deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting and cleaving the resulting intermediate (D')

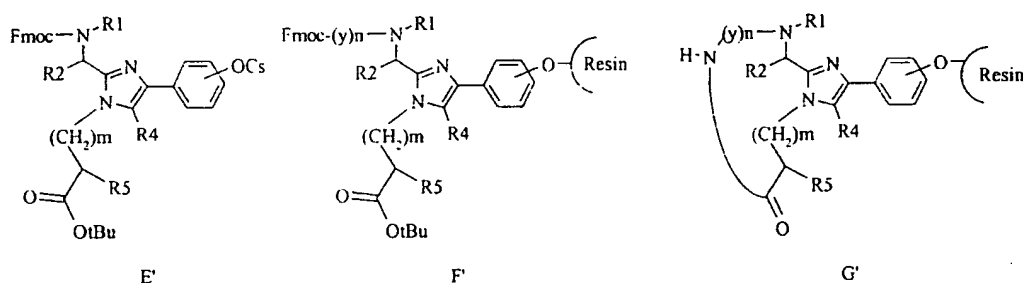
from the resin using a strong acid. and all other variables are as defined for formula (I) shown hereinabove. All variables are as defined for formula (I) shown hereinabove.



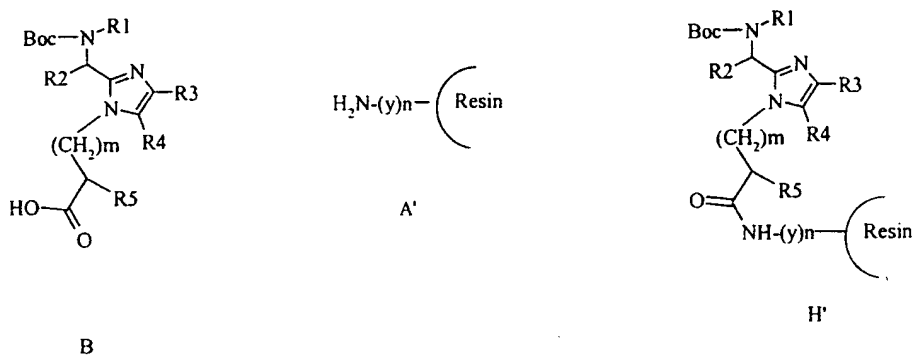
In another aspect, this invention provides a process for preparing a compound of formula (I), which comprises reacting a compound of formula (B) with a base, such as Cs₂CO₃, reacting the resulting phenolic cesium salt (E') with a halomethylated polystyrene resin, such as Merrifield peptide resin, removing the Fmoc protecting group with piperidine or similar organic base, acylating the liberated N-terminal

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amino group with an N_α -Fmoc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the base deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting the final protected peptide sequence at the N-terminus with piperidine or similar organic base and at the C-terminus with Tfa, cyclizing the resulting intermediate (F') using peptide coupling reactions well known to those familiar with the art, and cleaving the resulting intermediate (G') from the resin using a strong acid. All variables are as defined for formula (I) shown hereinabove.

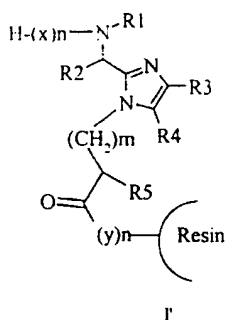


In another aspect, this invention provides a process for preparing a compound of formula (I), as defined hereinabove, which comprises coupling a compound of formula (B), activated as its active ester, anhydride, or acid halide, with an N-deprotected peptide-resin (A'), prepared by methods well known to those familiar with the art, deprotecting the N-terminal Boc group using Tfa, and deprotecting side chain protecting groups and cleaving the resulting intermediate (H') from the resin using a strong acid such as HF. All variables are as defined for formula (I) shown hereinabove.



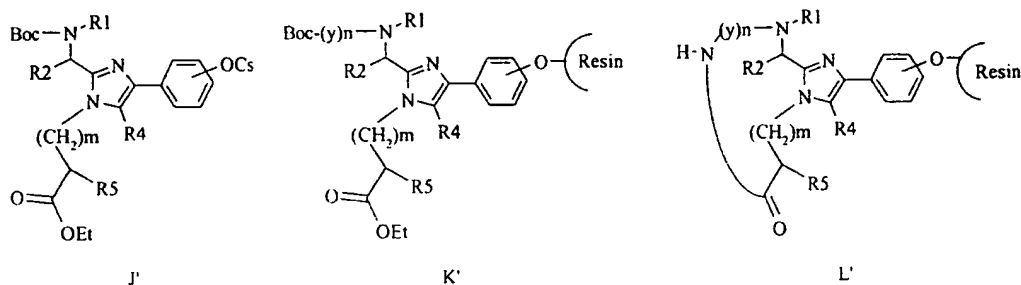
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In another aspect, this invention provides a process for preparing a compound of formula (I), which comprises coupling a compound of formula (B), activated as its active ester, anhydride, or acid halide, with an N-deprotected peptide-resin (H), prepared by methods well known to those familiar with the art, deprotecting the N-terminal Boc group using Tfa, acylating the liberated N-terminal amino group with an N_α-Boc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the Tfa deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting and cleaving the resulting intermediate (I') from the resin using a strong acid. All variables are as defined for formula (I) shown hereinabove.



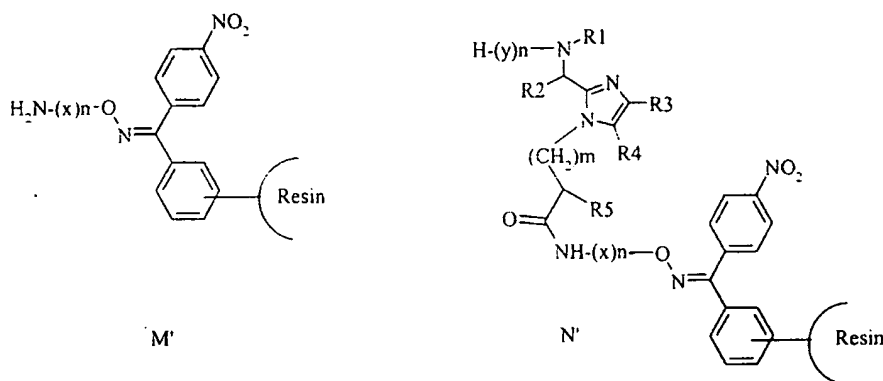
In another aspect, this invention provides a process for preparing a compound of formula (I), which comprises reacting a compound of formula (B) with a base, such as Cs₂CO₃, reacting the resulting phenolic cesium salt (J') with a halomethylated polystyrene resin, such as Merrifield peptide resin, removing the Boc protecting group with Tfa, acylating the liberated N-terminal amino group with an N_α-Boc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the Tfa deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting the final protected peptide sequence at the N-terminus with Tfa and at the C-terminus with an inorganic base such as LiOH in aqueous DMF, cyclizing the resulting intermediate (K') with using peptide coupling reactions well known to those familiar with the art, and cleaving the resulting intermediate (L') from the resin using a strong acid. All variables are as defined for formula (I) shown hereinabove.

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In another aspect, this invention provides a process for preparing a compound of formula (1), which comprises coupling a compound of formula (B), activated as its active ester, anhydride, or acid halide, with an N-deprotected peptide, 4-Nitrobenzophenone oxime resin (M'), prepared by methods well known to those familiar with the art, deprotecting the N-terminal Boc group using Tfa, acylating the liberated N-terminal amino group with an N_α-Boc-protected amino acid (x) using peptide coupling reactions well known to those familiar with the art, repeating the Tfa deprotection and coupling steps as required to incorporate additional amino acids (x), deprotecting the N-terminal Boc group with Tfa, cyclizing and cleaving the resulting intermediate N'-deprotected intermediate (N') by neutralizing with a suitable organic base, and removing side chain protecting groups with a strong acid, such as HF. All variables are as defined for formula (I) shown hereinabove.

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Detailed Description

The term heterocycle, as used herein, represents any heterocycle that may appear in the side chain of an amino acid. Examples include, but are not limited to, such heterocycles as benzothienyl, coumaryl, imidazolyl, indolyl, purinyl, pyridyl, pyrimidinyl, quinolinyl, thiazolyl, thienyl and triazolyl.

The term aryl, as used herein, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include biphenyl, indanyl, naphthyl, phenyl, and 1,2,3,4-tetrahydronaphthalene.

In the instant application several abbreviated designations are used for the amino acid components, certain preferred protecting groups, reagents and solvents. The meanings of such abbreviated designations are given in Table 1.

Abbreviated designation		Meaning
Amino acids	His	L-Histidine

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	Lys	L-Lysine
	Nal	L-3-(2-Naphthyl)-alanine
	Phe	L-Phenylalanine
	Ser	L-Serine
	Thr	L-Threonine
	Trp	L-Tryptophan (unless otherwise designated)
	Tyr	L-Tyrosine
	Ahx	6-aminohexanoic acid
Protecting groups	Boc	1,1-(Dimethylethoxy)carbonyl
	Cbz	Benzyloxycarbonyl
	Fmoc	9-Fluorenylmethoxycarbonyl
	Trt	Triphenylmethyl
Solvents	DMF	N,N-Dimethylformamide
	THF	Tetrahydrofuran
	EtOAc	Ethyl acetate
Reagents	Tfa	Trifluoroacetic acid
	NMM	4-Methylmorpholine
	DIEA	Diisopropylethylamine
	TEA	Triethylamine
	TAEA	Tris(2-aminoethyl)amine
	HOAT	1-Hydroxy-7-azabenzotriazole
	HATU	[O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	DCC	Dicyclohexylcarbodiimide

IN VITRO ASSAY

The affinity of a compound for human somatostatin subtype receptors 1 to 5 (sst₁, sst₂, sst₃, sst₄ and sst₅, respectively) is determined by measuring the inhibition of

5 [125I-Tyr¹¹]SRIF-14 binding to CHO-K1 transfected cells.

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The human *sst₁* receptor gene was cloned as a genomic fragment. A 1.5 Kb *Pst*I-*Xmn*I segment containing 100 bp of the 5'-untranslated region, 1.17 Kb of the entire coding region, and 230 bp of the 3'-untranslated region was modified by the *Bgl*II linker addition. The resulting DNA fragment was subcloned into the *Bam*HI site of a pCMV-81 to produce the mammalian expression plasmid (provided by Dr. Graeme Bell, Univ. Chicago). A clonal cell line stably expressing the *sst₁* receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method (1). The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

The human *sst₂* somatostatin receptor gene, isolated as a 1.7Kb *Bam*HI-*Hind*III genomic DNA fragment and subcloned into the plasmid vector pGEM3Z (Promega), was kindly provided by Dr. G. Bell (Univ. of Chicago). The mammalian cell expression vector is constructed by inserting the 1.7Kb *Bam*HI-*Hind*III fragment into compatible restriction endonuclease sites in the plasmid pCMV5. A clonal cell line is obtained by transfection into CHO-K1 cells using the calcium phosphate co-precipitation method. The plasmid pRSV-neo is included as a selectable marker.

The human *sst₃* was isolated as genomic fragment, and the complete coding sequence was contained within a 2.4 Kb *Bam*HI/*Hind*III fragment. The mammalian expression plasmid, pCMV-h3 was constructed by inserting the a 2.0 Kb *Nco*I-*Hind*III fragment into the *Eco*R1 site of the pCMV vector after modification of the ends and addition of *Eco*R1 linkers. A clonal cell line stably expressing the *sst₃* receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

The human *sst₄* receptor expression plasmid, pCMV-HX was provided by Dr. Graeme Bell (Univ. Chicago). The vector contains the 1.4 Kb *Nhe*I-*Nhe*I genomic fragment encoding the human *sst₄*, 456 bp of the 5'-untranslated region and 200 bp of the 3'-untranslated region, clone into the *Xba*I/*Eco*R1 sites of pCMV-HX. A clonal cell line stably expressing the *sst₄* receptor was obtained by transfection into CHO-

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K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

- 5 The human *sst₅* gene was obtained by PCR using a λ genomic clone as a template, and kindly provided by Dr. Graeme Bell (Univ. Chicago). The resulting 1.2 Kb PCR fragment contained 21 base pairs of the 5'-untranslated region, the full coding region, and 55 bp of the 3'-untranslated region. The clone was inserted into EcoR1 site of the plasmid pBSSK(+). The insert was recovered as a 1.2 Kb *HindIII*-
10 *XbaI* fragment for subcloning into pCVM5 mammalian expression vector. A clonal cell line stably expressing the SST₅ receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned,
15 and expanded into culture.

- CHO-K1 cells stably expressing one of the human *sst* receptor are grown in RPMI 1640 containing 10% fetal calf serum and 0.4 mg/ml geneticin. Cells are collected with 0.5 mM EDTA, and centrifuged at 500 g for about 5 min. at about 4°C. The pellet is resuspended in 50 mM Tris, pH 7.4 and centrifuged twice at 500 g for
20 about 5 min. at about 4°C. The cells are lysed by sonication and centrifuged at 39000 g for about 10 min. at about 4°C. The pellet is resuspended in the same buffer and centrifuged at 50000 g for about 10 min. at about 4°C and membranes in resulting pellet are stored at - 80°C.

- Competitive inhibition experiments of [¹²⁵I-Tyr¹¹]SRIF-14 binding are run in duplicate in polypropylene 96 well plates. Cell membranes (10 µg protein/well) are
25 incubated with [¹²⁵I-Tyr¹¹]SRIF-14 (0.05 nM) for about 60 min. at about 37°C in 50 mM HEPES (pH 7.4), 0.2% BSA, 5 mM MgCl₂, 200 KIU/ml Trasylol, 0.02 mg/ml bacitracin and 0.02 mg/ml phenylmethylsulphonyl fluoride.

- Bound from free [¹²⁵I-Tyr¹¹]SRIF-14 is separated by immediate filtration through
30 GF/C glass fiber filter plate (Unifilter, Packard) presoaked with 0.1 % polyethylenimine (P.E.I.), using Filtermate 196 (Packard) cell harvester. Filters are washed with 50 mM

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HEPES at about 0-4°C for about 4 sec. and assayed for radioactivity using Packard Top Count.

Specific binding is obtained by subtracting nonspecific binding (determined in the presence of 0.1 μ M SRIF-14) from total binding. Binding data are analyzed by computer-assisted nonlinear regression analysis (MDL) and inhibition constant (K_i) values are determined.

The determination of whether a compound of the instant invention is an agonist or an antagonist is determined by the following assay.

Functional assay: Inhibition of cAMP intracellular production:

10 CHO-K1 Cells expressing human somatostatin (SRIF-14) subtype receptors are seeded in 24-well tissue culture multidishes in RPMI 1640 media with 10% FCS and 0.4 mg/ml geneticin. The medium is changed the day before the experiment.

Cells at 10⁵ cells/well are washed 2 times by 0.5 ml and fresh RPMI with 0.2% BSA supplemented with 0.5 mM (1) 3-isobutyl-1-methylxanthine (IBMX) and 15 incubated for about 5 min at about 37°C.

- Cyclic AMP production is stimulated by the addition of 1mM forskolin (FSK) for about 15-30 minutes at about 37°C.
- The agonist effect of a compound is measured by the simultaneous addition of FSK (1 μ M), SRIF-14 (10⁻¹² M to 10⁻⁶ M) and a test compound (10⁻¹⁰ M to 10⁻⁵ M).
- 20 • The antagonist effect of a compound is measured by the simultaneous addition of FSK (1 μ M), SRIF-14 (1 to 10 nM) and a test compound (10⁻¹⁰ M to 10⁻⁵ M).

The reaction medium is removed and 200 μ l 0.1 N HCl is added. cAMP is measured using radioimmunoassay method (Kit FlashPlate SMP001A, New England Nuclear).

25 Radioligand Binding Assay

Membranes for *in vitro* receptor binding assays were obtained by homogenizing (Polytron, setting 6, 15 sec) the CHO-K1 cells, expressing the hsst receptor subtypes, in ice-cold 50 mM Tris-HCl and centrifuging twice at 39,000 g (10 min), with an intermediate resuspension in fresh buffer. The final pellets were 30 resuspended in 10 mM Tris-HCl for assay. For the hsst1, hsst3, hsst4, hsst5 assays, aliquots of the membrane preparations were incubated (for about 30 min at about 37 °C with 0.05 nM [125I-Tyr11]SRIF-14 in 50 mM HEPES (pH 7.4) containing

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BSA (10 mg/ml); MgCl₂ (5 mM)), Trasylol (200 KIU/ml), bacitracin (0.02 mg/ml), and phenylmethanesulphonyl fluoride (0.02 mg/ml). The final assay volume was 0.3 ml.

For the *hsst2* assay, [¹²⁵I]MK-678 (0.05 nM) was employed as the radioligand and the incubation time was about 90 min at about 25 °C. The incubations were terminated by rapid filtration through GF/C filters (pre-soaked in 0.3% polyethylenimine) using a Brandel filtration manifold. Each tube and filter were then washed three times with 5-ml aliquots of ice-cold buffer.

Specific binding was defined as the total radioligand bound minus that bound in the presence of 1000 nM SRIF-14(*hsst1,3,4,5*), or 1000 nM MK-678 for *hsst2*.

The compounds of the instant invention can be *in vivo* assayed for the uses associated with binding to the somatostatin receptor, including specificity binding to the somatostatin subtype receptor(s), according to methods well known to those skilled in the art as exemplified by the following references: I. Shimon, et. al., "Somatostatin receptor subtype specificity in human fetal pituitary cultures", J. Clin. Invest., Vol. 99, No.4, pp. 789-798, 1997; and C. Gilon, et. al., "A backbone-cyclic, receptor 5-selective somatostatin analogue: Synthesis, bioactivity, and nuclear magnetic resonance conformational analysis", J. Med. Chem. 1998, 41, 919-929.

As is well known to those skilled in the art, the known and potential uses of somatostatin agonists and/or antagonists are varied and multitudinous. These varied uses of somatostatin may be summarized as follows:

Somatostatin agonists can be used to suppress growth hormone and more particularly GH secreting adenomas (acromegaly) and TSH secreting adenomas; treat prolactin secreting adenomas; inhibit insulin and/or glucagon and more particularly diabetes mellitus, angiopathy, proliferative retinopathy, dawn phenomenon and nephropathy; inhibition of gastric acid secretion and more particularly peptic ulcers; enterocutaneous and pancreaticocutaneous fistula; irritable bowel syndrome; Dumping syndrome; watery diarrhea syndrome; AIDS related diarrhea; chemotherapy-induced diarrhea; acute or chronic pancreatitis and gastrointestinal hormone secreting tumors; treatment of cancer such as hepatoma; inhibition of angiogenesis; treatment of inflammatory disorders such as arthritis;

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retinopathy; chronic allograft rejection; angioplasty; preventing graft vessel and gastrointestinal bleeding.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the instant invention as described herein in association with a pharmaceutically acceptable carrier.

A compound of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the

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compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories
5 which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained
10 release composition such as those described in the following patents. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a
15 bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. The teachings of the foregoing patents and applications are incorporated herein by reference.

20 The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg of body weight
25 daily are administered to humans and other animals, e.g., mammals, to obtain a therapeutic effect.

A preferred dosage range is 0.01 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

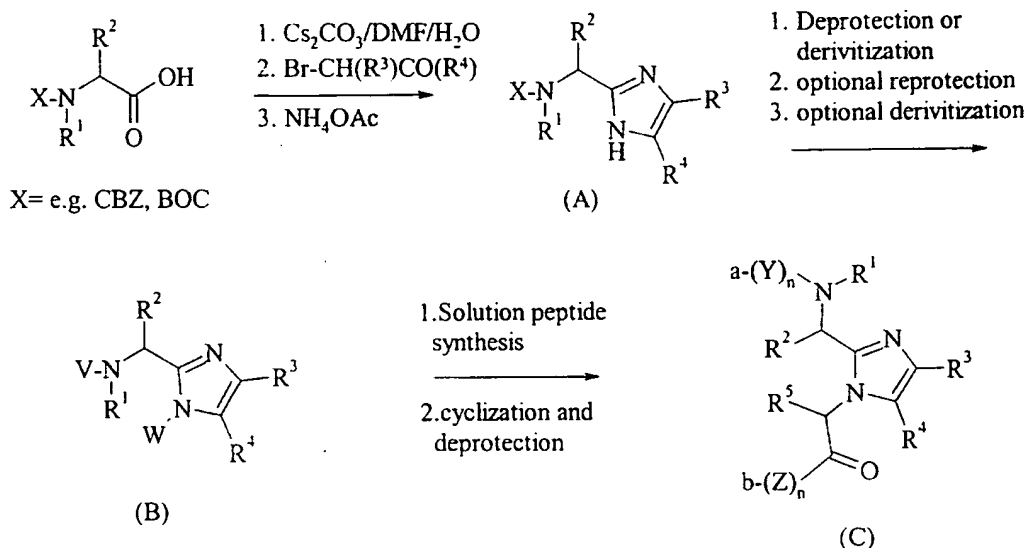
A compound of this invention can be synthesized according to the following
30 description and Scheme I. In a first step, an amino acid, protected on the α -amino group with Boc, Cbz or other suitable group, is converted to a carboxylate salt with an inorganic base, for example NaOH, KOH, K_2CO_3 , or most preferably Cs_2CO_3 , in a

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polar solvent such as H₂O, DMF, THF, or the like. The solvent is removed under vacuum and the residual salt is re-dissolved in a polar aprotic solvent such as DMF and a suitable α -halo ketone is added with stirring at about -20°C to about 100°C, most preferably at room temperature. Stirring is continued for about 10
5 minutes to about 24 hours, or until ester formation is complete by TLC analysis, at which time the solution is concentrated under vacuum at about 0°C to about 100°C, most preferably at about 40°C to about 70°C. The intermediate is re-dissolved in an aprotic organic solvent such as benzene, toluene or, most preferably, xylenes, and about 5-fold to about 100-fold or, most preferably about 15-20 fold molar excess of
10 NH₄OAc is added. The two phase mixture is heated at reflux and the polar layer is completely removed over the course of about 1 to about 4 hours by means of a Dean-Stark trap to give crude intermediate (A) which may be used crude or purified by crystallization or column chromatography.

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Scheme I



In a second step, intermediate (A) is deprotected using catalytic hydrogenation or strong acids such as HF, HCl, HBr or Tfa. The α -nitrogen may then be protected with a base sensitive protecting group such as the Fmoc group using commercially available N-(9-fluorenylmethoxycarbonyloxy)succinimide and K_2CO_3 in, for example, acetonitrile and water. Alternatively, the N_α -Cbz-protected imidazole nitrogen may be alkylated with a protected carboxylic ester halide and deprotected on the α -amino group using catalytic hydrogenation to yield B' (V=H, W=

5 10 15 20

-(CH₂)_mCR⁵CO₂R', where R' represents an alkyl or benzylic ester). The imidazole nitrogen may be protected using commercially available triphenylmethyl chloride and a tertiary amine base such as 4-methyl-morpholine, diisopropylethylamine or triethylamine to yield an Fmoc-protected intermediate which is subsequently deprotected on the α -amino group using bases such as, for example, TAEA to yield intermediate (B) (V=H, W=Trt). Alternatively, the N-deprotected imidazole B'' (V=H, W=H) may be used without further modification.

In a third step, intermediate B, B', or B'' is used as an anchor group for the continuous solution phase synthesis of a target peptide. Thus, the anchor group is dissolved in ethyl acetate at a concentration of about 50-200 mmol per liter and about 1 to 5 molar equivalents or, more preferably, 1.1 to 1.5 molar equivalents of an

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N_α -Fmoc protected amino acid, in the form of its activated ester, anhydride or acid halide is added. The mixture is stirred over a second layer of weak base such as aqueous Na_2CO_3 or, more preferably, aqueous NaHCO_3 solution until the reaction is complete. The aqueous layer is removed and about 1 to 10 ml/mmol or, more preferably, about 2-4 ml/mmol of TAEA or piperidine is added and the mixture is stirred for about 30 minutes. The solution is then washed with saturated NaCl solution (2 times with about 30 ml/mmol) and then with 10% phosphate buffer solution adjusted to pH=5.5 (3 times with about 10 ml/mmol). Subsequent cycles are performed in a manner similar to the first cycle. The final amino acid may be protected on N_α with a Boc or an Fmoc group.

In a fourth step, the N-terminal and C-terminal protecting groups are removed with aqueous base or with strong acids, and the resulting peptide intermediate may be cyclized using classical peptide coupling techniques as described in "The Practice of Peptide Synthesis", Bodanszky and Bodanszky, Springer-Verlag, 1984. Accordingly, the peptide intermediate is dissolved in an aprotic solvent such as DMF and the solution is made basic by addition of tertiary amine base such as 4-methylmorpholine. The carboxylate portion of the intermediate is activated by addition of a 1- to 6-fold molar excess of a carbodiimide, such as DCC or EDC, and an additive such as, for example, 1-hydroxybenzotriazole. The mixture is stirred at about 0° to 100°C, most preferably at about room temperature, until the reaction is complete.

In a final step, the protected peptide is freed of protecting groups using catalytic hydrogenation or strong acids such as HF, HCl, HBr or Tfa to yield final product (C), where R^1 to R^5 , a, b, Y, Z, and n are as defined above for formula (I).

The infusion mass spectral data was measured on a Finnigan SSQ 7000 spectrometer equipped with an ESI (electrospray ionization) source. NMR data was obtained on a 300MHz Varian Unity spectrometer from samples at concentrations of about 10-20mg/ml in the designated solvents.

Alternatively, compounds of the present invention can be prepared using solid phase peptide synthesis techniques. Thus, intermediate A (X=Boc) is alkylated with, for example, ethyl bromoacetate and a suitable base, for example, K_2CO_3 in an aprotic solvent, for example, DMF, and the resulting ethyl ester

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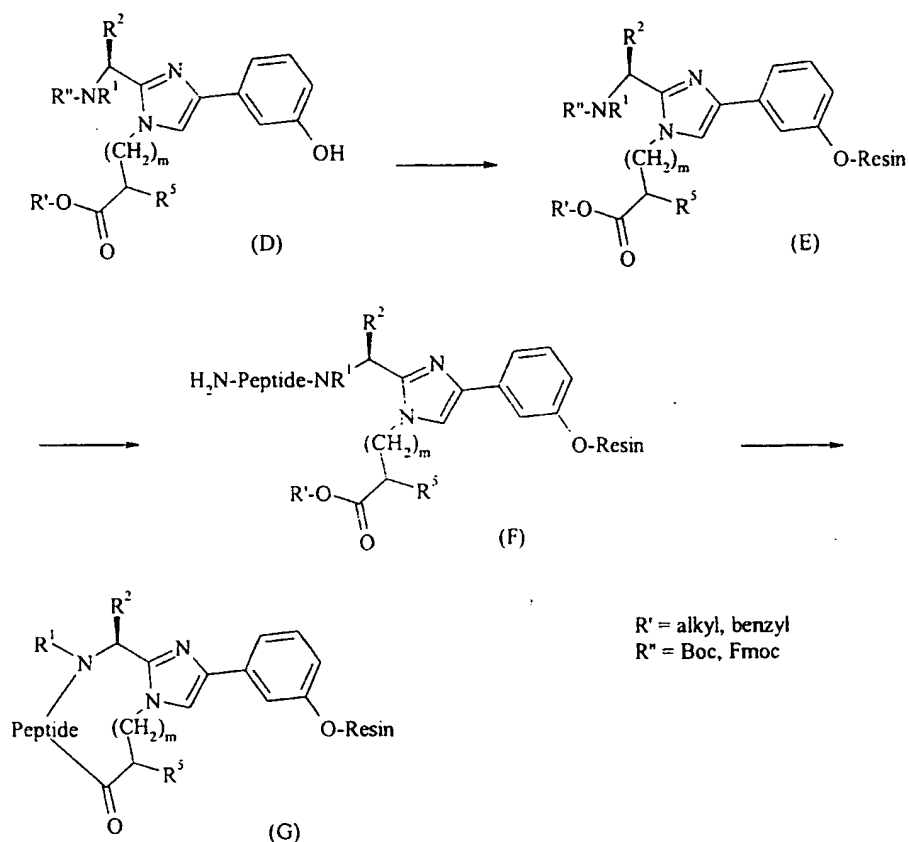
intermediate is hydrolyzed using an aqueous base, for example, NaOH, to provide intermediate B (V=Boc, W= -CH₂CO₂H). Intermediate B (V=Boc, W= -CH₂CO₂H) can be activated using known activation techniques as described in "The Practice of Peptide Synthesis", Bodanszky and Bodanszky, Springer-Varlag, 1984, and used directly for coupling to the growing peptide on a solid support or, intermediate B (V=Boc, W= -CH₂CO₂H) may be attached directly to the solid support to begin a solid phase synthesis. Deprotection of the N-terminal Boc group with, for example, Tfa, allows the continuation of peptide synthesis under conditions known to one of ordinary skill in the art.

Intermediate B (V=Fmoc, W= -CH₂CO₂t-Bu, for example) can be treated with acid, for instance, Tfa to remove the carboxylate protecting t-butyl ester and the resulting intermediate B (V=Fmoc, W= -CH₂CO₂H, for example) can be used for solid phase peptide synthesis using the Fmoc strategy. Thus, Intermediate B (V=Fmoc, W= -CH₂CO₂H) can be activated using known activation techniques as described in "The Practice of Peptide Synthesis", M. Bodanszky and A. Bodanszky, Springer-Varlag, 1984, and used directly for coupling to the growing peptide on a solid support. Deprotection of the N-terminal Fmoc group with, for instance, piperidine allows the continuation of peptide synthesis under conditions known to one of ordinary skill in the art.

The solid phase synthesis of cyclic analogs can also be carried out, according to Scheme II, below.

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SCHEME II



- Intermediate A ($X = \text{Boc}$ or Cbz , $R^3 = 2\text{-methoxyphenyl}$, 3-methoxyphenyl or 4-methoxyphenyl) can be treated with 1M BBr_3 in CH_2Cl_2 for about $\frac{1}{2}$ hour to provide the free phenol A ($X = \text{H}$, $R^3 = 2\text{-hydroxyphenyl}$, 3-hydroxyphenyl or 4-hydroxyphenyl). The α -nitrogen may then be protected with an acid sensitive protecting group such as the Boc group using di-*t*-butyldicarbonate and a base, for example, NaOH in a mixture of an organic, water miscible solvent, for example, dioxane and water.
- Intermediate A ($X = \text{Boc}$, $R^3 = 2\text{-hydroxyphenyl}$, 3-hydroxyphenyl or 4-hydroxyphenyl) is alkylated with, for example, ethyl bromoacetate and a suitable base, for example, K_2CO_3 in an aprotic solvent, for example, DMF, to provide the resulting ethyl ester intermediate D. Intermediate D is then converted to its cesium salt by the action of cesium carbonate. The cesium salt is reacted, in excess, with Merrifield resin to provide intermediate E. Intermediate E is subject to elaboration using standard Boc

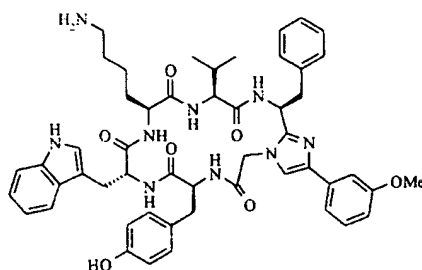
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solid phase peptide synthesis or standard Fmoc solid phase synthesis as previously described to yield intermediate F. When the complete amino acid sequence has been constructed, the C-terminal ethyl ester is unmasked using a suitable base, for example, LiOH in aqueous DMF and the peptide is cyclized using a standard activation protocol, for example, a carbodiimide with, for example, hydroxybenzotriazole and a tertiary amine base, for example, diisopropylethyl amine to provide intermediate G. Final side chain deprotection and cleavage from the resin is realized by addition of a very strong acid, for example, HF to yield compounds of the invention.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

EXAMPLE 1

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]



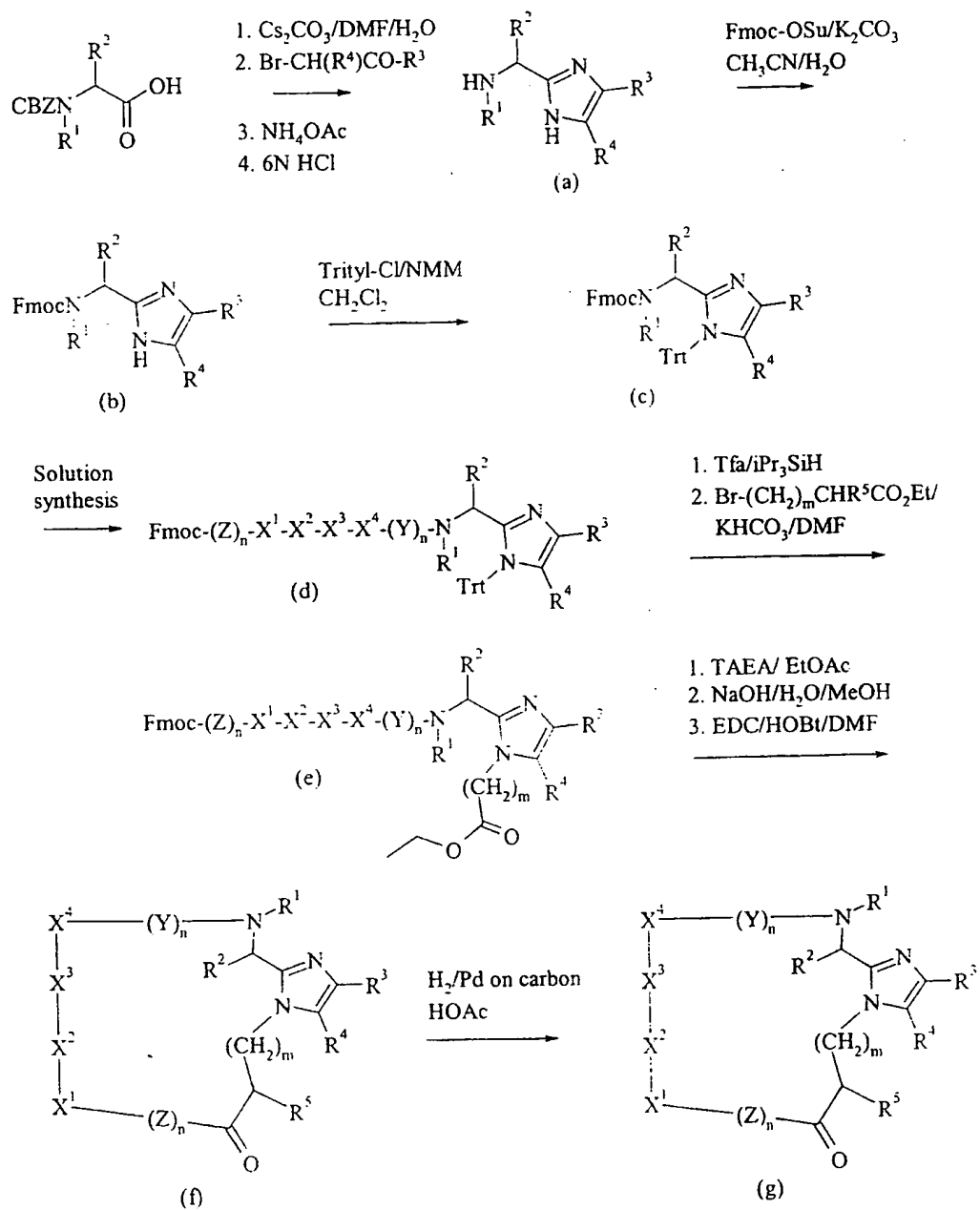
Example 1 was synthesized according to synthetic scheme 1 as shown below:

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Example 1 was synthesized according to synthetic scheme 1 as shown

below:

SCHEME 1



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Step a: 2-(1-(S)-amino-2-phenylethyl)-4-(3-methoxyphenyl)-imidazole

Cbz-(L)-Phenylalanine (10.0g, 33.4mmol) and Cs_2CO_3 (5.44g, 16.7mmol) were combined in 2:1 / DMF:H₂O (75 ml) and the mixture was swirled until
5 homogeneous. Solvents were removed under reduced pressure, the residue was dissolved in DMF (70ml) and 2-bromo-3'-methoxyacetophenone (7.65g, 33.4mmol) in DMF (30ml) was added. The mixture was stirred for about 30 min. at room temperature then concentrated under reduced pressure. The resulting keto-ester was dissolved in xylenes (150ml) and the CsBr was filtered off. Ammonium acetate
10 (40.0g, 0.52 mole) was added and the mixture was heated at reflux for about 2 hours with removal of excess NH₄OAc and liberated H₂O using a Dean-Stark trap. The reaction was cooled and washed with saturated NaHCO₃ solution (50ml) and saturated NaCl solution (50ml). The xylenes layer was dried over Na₂SO₄, filtered and concentrated under vacuum.

15 The residue was dissolved with dioxane (30ml), 6N HCl (115ml) was added and the mixture heated at reflux for about 3 hours. The solution was concentrated under vacuum and triturated with ethyl ether (4X100ml). The residue was dried to constant weight under vacuum to yield 12.15g (99%) of intermediate 1a, mass spec. 294.2 MH⁺.

20 Step b: 2-(1-(S)-((Fluorenylmethoxy)carbonyl)amino-2-phenylethyl)-4-(3-methoxyphenyl)-imidazole

Intermediate 1a (11.8g, 32.2mmol) was dissolved in 1:1/acetonitrile:H₂O (200ml) and K₂CO₃ (5.38g, 39mmol) was cautiously added in portions. 9-Fluorenylmethyl-succinimidylcarbonate was added and the resulting mixture was
25 stirred vigorously for about 20 minutes. Product was extracted with EtOAc (100ml) and the EtOAc layer was washed with H₂O (2X50ml). The EtOAc layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The product was purified by flash chromatography on silica gel (150g) eluting with 2:2:1/CH₂Cl₂:hexanes:EtOAc and then with 1:1/ hexanes:EtOAc. Product fractions were pooled and concentrated
30 under vacuum to a yield intermediate 1b as a pale yellow foam, 14.77g (85%). Mass spec. 516.3 MH⁺, NMR (300MHz, DMSO-d₆), 11.8-12.0 (1H, s), 7.8-8.0 (3H, d), 7.6-

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7.8 (2H, d), 7.5 (1H, s), 7.1-7.5 (12H, m), 6.7-6.9 (1H, d) 4.8-5.0 (1H, m), 4.1-4.3 (3H, m), 3.7-3.9 (3H, s), 3.0-3.4 (2H, m).

Step c: 2-(1-(S)-((Fluorenylmethoxy)carbonyl)amino-2-phenylethyl)-4-(3-methoxyphenyl)-1-triphenylmethyl-imidazole

5 Intermediate 1b (13.9g, 26.9mmol) was dissolved in CH₂Cl₂ (50ml) under N₂, 4-methylmorpholine (2.96ml, 26.9mmol) and chlorotriphenylmethane (7.51g, 26.9mmol) were added and the solution was allowed to stir at room temperature for about 45 minutes. Solids were removed by filtration and the filtrate purified by flash chromatography on silica gel (300g) using 70:30/ hexanes:EtOAc as eluant. Product
10 fractions were combined and concentrated under vacuum to yield intermediate 1c as a foam, 18.0g (88%), NMR (300MHz, DMSO-d₆), 7.84-7.95 (2H,d), 7.7-7.8 (1H, d), 7.6-7.7 (1H, d), 6.7-7.5 (29H, m), 4.3-4.5 (1H, m), 3.75-3.95 (2H, m) 3.75-3.85 (3H, s), 3.6-3.7 (1H, m), 2.65-2.85 (1H, d,d), 2.05-2.2 (1H, m).

Step d: 2-(1-(S)-((Fmoc-Tyr(OBzl)-D-Trp-Lys(Cbz)-Val)amino-2-phenylethyl)-4-(3-methoxyphenyl)-1-(triphenylmethyl)-imidazole
15

Intermediate 1c (1.89g, 2.50mmol) was dissolved in EtOAc (40ml), Tris(2-aminoethyl)amine (9ml) was added and the mixture stirred vigorously for about ½ hour. The EtOAc layer was washed with saturated NaCl solution (2 X 120ml) and then with 10% phosphate buffer solution adjusted to about pH=5.5 (3 X 40ml). The
20 EtOAc layer was stirred over saturated NaHCO₃ solution (40ml) and Fmoc-Val-F (1.02g, 3.00 mmole) was added. The reaction was stirred for about 1 hour and the aqueous layer was removed.

The intermediate was then sequentially deprotected and coupled with Fmoc-Lys(Cbz)-OSu, Fmoc-D-Trp-OSu and Fmoc-Tyr(OBzl)-OSu in a manner similar to
25 the Fmoc-Val-F cycle described immediately above. The EtOAc layer was diluted with 1.5 volumes of hexanes and applied to a silica gel column for purification by flash chromatography using 50:30:20/CH₂Cl₂:EtOAc:hexanes first and then with 4:1/ EtOAc:hexanes as eluants. Product fractions were pooled and concentrated under vacuum to yield intermediate 1d as a white foam, 1.90g, (46%). Mass spec 1581.2
30 MNa⁺, 1559.5 MH⁺.

Step e: 1-((2-Ethoxy-2-oxo)ethyl)-2-(1-(S)-((Fmoc-Tyr(OBzl)-D-Trp-Lys(Cbz)-Val)amino-2-phenylethyl)-4-(3-methoxyphenyl)-imidazole

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Intermediate 1d (519mg, 0.33mmol) was dissolved in Tfa (10ml) containing $i\text{Pr}_3\text{SiH}$ (205ul, 1.0mmol) and the mixture was stirred for about 15 minutes. Intermediate was precipitated by addition of ethyl ether (60ml) and filtered off. Mass spec 1316 MH⁺. The intermediate was dissolved in DMF (3ml), KHCO_3 (198mg, 2.0mmol) and ethyl bromoacetate (721ul, 6.5mmol) were added and the mixture was stirred overnight at room temperature. The mixture was concentrated under vacuum, dissolved in CH_2Cl_2 (10ml) and washed with H_2O (10ml). The CH_2Cl_2 layer was dried over Na_2SO_4 , filtered and concentrated under vacuum to yield crude intermediate 1e (540mg) which was used without further purification.

10 Step f: cyclo [Tyr(OBzl)-D-Trp-Lys(Cbz)-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Intermediate 1e (540mg, 0.33mmol) was suspended in EtOAc (10ml) and tris(aminoethyl)amine (1ml) was added and the mixture was stirred vigorously for about ½ hour. EtOAc (10ml) was added and the solution was washed with saturated NaCl solution (2X25ml) and then with 10% phosphate buffer solution (pH=5.5, 3X10ml). The intermediate was precipitated by addition of hexanes (40ml), and the solvents were decanted. The residue was dissolved in methanol (10ml) and stirred overnight at room temperature with 2.5N NaOH (0.5ml). The mixture was diluted to turbidity with H_2O and the pH was adjusted to about 6.7. The deprotected intermediate was filtered off and dried under vacuum. The solid was taken up in DMF (25ml) and DCC (340mg, 1.65mmol) and HOBt (252mg, 1.65mmol) were added. The mixture was stirred at room temperature for about 2 hours and concentrated under reduced pressure. Crude product was purified by flash chromatography on silica gel using EtOAc as eluant. Product fractions were combined and concentrated under vacuum to yield intermediate 1f as a glass (180mg, 48% from intermediate 1d). Mass spec 1134.5 MH⁺.

25 Step g: cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Intermediate 1f (180mg, 0.16mmol) was dissolved in acetic acid (10ml) containing 10% Pd on carbon (24mg) and the mixture was shaken under H_2 (25psi) at room temperature for about 8 hours. The catalyst was filtered off and the residue concentrated under vacuum. The crude mixture was composed of completely deprotected material (both Cbz and benzyl ether removed) and partially deprotected

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material (Cbz removed and benzyl ether intact). The mixture was purified by preparative HPLC on a VYDAC® Protein & Peptide C₁₈ column (The Nest Group Inc., Southborough, MA) using a gradient of 20% to 70% CH₃CN/ 0.1% Tfa over about 55 minutes. Pure fractions of the more polar peak were combined, concentrated, and lyophilized (2X10ml 0.5% HCl, then 1X10ml H₂O) to yield the title compound of Example 1, 45mg (29%). Mass spec. 910.4 MH⁺.

Example 2

cyclo [Tyr(OBzl)-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Example 2 was prepared substantially according to synthetic scheme 1, Example 1, but using the appropriate amino acids. Pure fractions of the less polar peak from the purification of 1g were combined, concentrated, and lyophilized (2X10ml 0.5% HCl, then 1X10ml H₂O) to yield the title product of Example 2, 33mg (21%). Mass spec. 1000.4 MH⁺.

Example 3

cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Example 3 was prepared according to synthetic scheme 1 in a manner substantially similar to Example 1 but with the following differences:

Step d: 2-(1-(S)-((Fmoc-Trp-D-Trp-Lys(Cbz)-Val)-amino-2-phenylethyl)-4-(3-methoxyphenyl)-1-(triphenylmethyl)-imidazole

Intermediate 1c (757mg, 1.0mmol) was dissolved in EtOAc (20ml), tris(2-aminoethyl)amine (3ml) was added and the mixture stirred vigorously for about ½ hour. The EtOAc layer was washed with saturated NaCl solution (2 X 60ml) and then with 10% phosphate buffer solution adjusted to a pH of about 5.5 (3 X 20ml). The EtOAc layer was stirred over saturated NaHCO₃ solution (20ml) and Fmoc-Val-F (825mg, 2.33mmol) was added. The reaction was stirred for about 1 hour and the aqueous layer was removed.

The intermediate was sequentially deprotected and coupled with Fmoc-Lys(Cbz)-OSu, Fmoc-D-Trp-OSu and Fmoc-Trp-OSu in a manner similar to the Fmoc-Val-F cycle described immediately above. The EtOAc layer was diluted with 1.5 volumes of hexanes and applied to a silica gel column for purification by flash chromatography using 50:30:20/CH₂Cl₂:EtOAc:hexanes first and then with 4:1/ EtOAc:hexanes as eluants. Product fractions were pooled and concentrated under

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vacuum to yield intermediate 3d as a white foam, 1.02g, (68%). Mass spec 11492.0 MNa⁺, 1514.2 MH⁺.

Step e: 1-((2-Ethoxy-2-oxo)ethyl)-2-(1-(S)-((Fmoc-Trp-D-Trp-Lys(Cbz)-Val)-amino-2-phenylethyl)-4-(3-methoxyphenyl)-imidazole

5 Intermediate 3d (1.00g, 0.67mmol) was dissolved in a mixture of CH₂Cl₂ (10ml), Tfa (1ml) and iPr₃SiH (205ul, 1.0mmol) and the mixture was stirred for about 20 minutes. A mixture of 1:1/Et₂O:hexanes (100ml) was added and the intermediate was filtered off and dried (0.88g). The intermediate was dissolved in DMF (10ml), KHCO₃ (200mg, 2.00mmole) and ethyl bromoacetate were added and the reaction
10 was stirred overnight at room temperature. The mixture was concentrated under reduced pressure to yield intermediate 3e which was used without further purification. Mass spec 1335.7 MH⁺

Step f: cyclo [Trp-D-Trp-Lys(Cbz)-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Intermediate 3e (crude, 0.67mmol) was dissolved in methanol (10ml) and
15 stirred at room temperature with 2.5N NaOH (1.0ml) for about 45 minutes. The mixture was diluted to turbidity with H₂O and the pH was adjusted to 6.9. Solvents were decanted and the residue was triturated with H₂O to yield a pale yellow powder (650mg, mass spec 1085.5 MH⁺). The powder (629mg) was dissolved in DMF (20ml) then NMM (220ul, 2.0mmol), EDC (192mg, 1.0mmol) and HOBt (153mg,
20 1.0mmol) were added. The mixture was stirred at room temperature for about 2 hours and concentrated under vacuum. Crude product was dissolved in CH₂Cl₂ (15ml) and washed with 10% phosphate buffer solution (adjusted to pH=5.5). The CH₂Cl₂ layer was dried over Na₂SO₄, filtered and concentrated to 2 ml. Ethyl ether was added to precipitate the product, which was filtered off and dried to yield
25 intermediate 3f (440mg, 71%). Mass spec 1067.4 MH⁺.

Step g: cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Intermediate 3f (200mg, 0.19mmol) was dissolved in acetic acid (15ml) containing 10% Pd on carbon (40mg) and the mixture was shaken under H₂ (25psi) at room temperature for 2 days. The catalyst was filtered off and the residue
30 concentrated under vacuum. The crude mixture was purified by preparative HPLC on a C₁₈ column (Rainin Microsorb™ 80-220-C5) using a gradient of 20% to 70% CH₃CN/ 0.1% Tfa over about 55 minutes. A second pass using a gradient of 30% to

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50% CH₃CN/ 0.1% Tfa over about 55 minutes was required to obtain good separation. Pure fractions were combined, concentrated, and lyophilized (2X10ml 0.5% HCl, then 1X10ml H₂O) to yield the title compound of Example 3, 26mg (14%). Mass spec. 933.5 MH⁺.

5

Example 4

cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

Example 4 was prepared according to synthetic scheme 1 in a manner substantially similar to that of Example 1 with the following differences:

Step g: cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

10

Intermediate 3f (150mg, 0.14mmol) was dissolved in CH₂Cl₂ (12ml) and a solution of 1M BBr₃ in hexanes was added under N₂. The resulting slurry was stirred for about ½ hour. Methanol (10ml) was added and the mixture was concentrated under vacuum. The crude mixture was purified by preparative HPLC on a C₁₈ column using a gradient of 24% to 48% CH₃CN/ 0.2 % NH₄OAc over about 50 minutes. Pure fractions were combined, concentrated, and lyophilized (2X10ml H₂O) to yield the title compound of Example 4, 40mg (29%). Mass spec. 919.4 MH⁺.

15

Example 5

cyclo [Trp-D-Trp-Lys-Thr(Obzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Example 5 was prepared according to scheme 1 in a manner substantially similar to Example 3 except that Fmoc-Thr(Obzl)-F was used in place of Fmoc-Val-F in step d. Mass spec 1025.5 MH⁺.

20

Example 6

cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

Example 6 was prepared according to scheme 1 in a manner substantially analogous to Example 4 except that intermediate 5f, cyclo[Trp-D-Trp-Lys(Cbz)-Thr(Obzyl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly], was used in place of intermediate 3f in step g. Mass spec 1025.5 MH⁺.

25

Example 7

H-Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly-OH

Example 7 was prepared according to scheme 1 in a manner substantially analogous to Example 3 except that Fmoc-Abu-F was used in place of Fmoc-Val-F in

30

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step 3d and cyclization with carbodiimide and HOBt was not performed in step 3f. Mass spec 937.3 MH⁺.

Example 8

cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

5 Example 8 was prepared according to scheme 1 in a manner substantially analogous to Example 3 except that Fmoc-Abu-F was used in place of Fmoc-Val-F in step 3d. Mass spec 919.5 MH⁺.

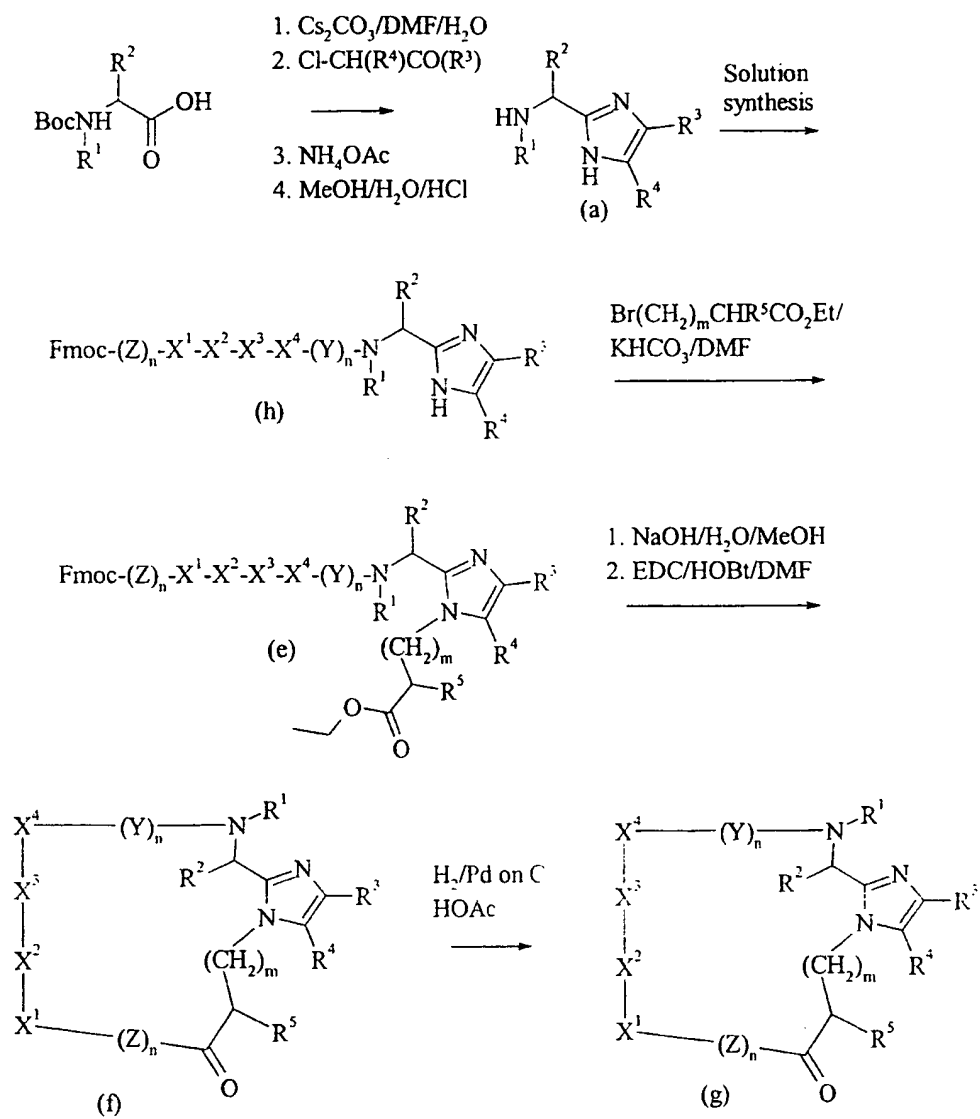
Example 9

cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole)-Gly]

10 Example 9 was prepared according to Scheme 2.

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SCHEME 2



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Step a. 2-(1-(S)-amino-2-phenylethyl)-4-(1,1-dimethylethyl)-imidazole

Boc-(L)-Phenylalanine (5.31g, 20.0mmol) and Cs_2CO_3 (3.26g, 10.0mmol) were combined in 1:1/DMF:H₂O (50 ml) and the mixture was swirled until a homogeneous mixture was obtained. Solvents were removed under reduced pressure and the residue was dissolved in DMF (50ml) and 1-chloropinacolone (2.63ml, 20.0mmol) was added. The mixture was stirred overnight at room temperature then concentrated under reduced pressure. The resulting keto-ester was dissolved in xylenes (100ml) and the CsBr was filtered off. Ammonium acetate (25.0g, 0.33 mol) was added and the mixture was heated at reflux for about 2 hours with removal of excess NH₄OAc and liberated H₂O using a Dean-Stark trap. The reaction was cooled and washed with saturated NaHCO₃ solution (50ml), dried over Na₂SO₄, filtered and concentrated under vacuum. Purification of the protected intermediate by flash chromatography on silica gel using 80:20/hexanes:EtOAc as eluant yielded 3.45g (50%) of a crystalline intermediate (Mass spec 344.3 MH⁺). This intermediate was dissolved with methanol (30ml), and conc. HCl (5.0ml) was added and the mixture stirred for about 3 hours. The solution was concentrated under vacuum and the residue precipitated from THF and ethyl ether. The solid was dried under vacuum to yield 1.89g (95%) of intermediate 9a. NMR (300MHz, DMSO-d₆), 8.5-10.5 (3H, broad s), 7.3-7.4 (1H, s), 7.15-7.35 (3H, m), 7.0-7.1 (2H, m), 4.9-5.1 (1H, t), 3.5-3.65 (2H, d), 1.2-1.3 (9H, s).

Step b. 2-(1-(S)-((Fmoc-Phe-D-Trp-Lys(Boc)-Tyr(OBzl))-amino-2-phenylethyl)-4-(1,1-dimethylethyl)-1H-imidazole

Intermediate 9a (790mg, 2.50mmol) was dissolved in EtOAc (40ml), tris(2-aminoethyl)amine (9ml) was added and the mixture stirred vigorously for about ½ hour. The EtOAc layer was washed with saturated NaCl solution (2 X 120ml) and then with 10% phosphate buffer solution adjusted to about pH=5.5 (3 X 40ml). The EtOAc layer was stirred over saturated NaHCO₃ solution (40ml) and FmocTyr(OBzl)-OSu (1.02g, 3.00 mmol) was added. The reaction was stirred for about 1.5 hour and the aqueous layer was removed.

The intermediate was sequentially deprotected and coupled with Fmoc-Lys(Cbz)-OSu, Fmoc-D-Trp-OSu and Fmoc-Phe-OSu in a manner similar to the

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Fmoc-Tyr(OBzl)-OSu cycle described immediately above. The EtOAc layer was applied to a silica gel column for purification by flash chromatography using 1% acetic acid/EtOAc as eluant. Product fractions were pooled and concentrated under vacuum. The crude product was redissolved in EtOAc, precipitated by addition of hexanes and filtered off. The solid was dried under vacuum to yield intermediate 9h, 1.67g, (52%). Mass spec 1280.7 MH⁺.

Step e: 4-(1,1-dimethylethyl)-2-(1-(S)-((Fmoc-Phe-D-Trp-Lys(Boc)-Tyr(OBzl)-amino-2-phenylethyl)-1-(2-ethoxy-2-oxo-ethyl)-imidazole

Intermediate 9h (128mg, 0.10mmol) was dissolved in DMF (2ml), K₂CO₃ (35mg, 0.25mmol) and ethyl bromoacetate (28ul, 0.25mmol) were added and the mixture was stirred overnight at room temperature. The mixture was concentrated under vacuum, dissolved in EtOAc (10ml) and washed with H₂O (10ml). The EtOAc layer was dried over Na₂SO₄, filtered and concentrated under vacuum to yield crude intermediate 9e (126mg, 92%) which was used without further purification.

Step f: cyclo [Phe-D-Trp-Lys(Boc)-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

Intermediate 9e (116mg, 0.085mmol) was suspended in EtOAc (2ml) and tris(aminoethyl)amine (0.5ml) was added and the mixture was stirred vigorously for about ½ hour. EtOAc (10ml) was added and the solution was washed with saturated NaCl solution (2X5ml) and then with 10% phosphate buffer solution (pH=5.5, 3X5ml). The intermediate was precipitated by addition of hexanes (40ml), and the intermediate was filtered off (76mg). The residue was dissolved in methanol (2ml) and stirred overnight at room temperature with 2.5N NaOH (0.1ml). The mixture was diluted to turbidity with H₂O and the pH was adjusted to about 6.0. The deprotected intermediate was filtered off and dried under vacuum. The solid was taken up in DMF (20ml) and DCC (126mg, 0.60mmole) and HOBt (90mg, 0.60mmol) were added. The mixture was stirred at room temperature for about 6 hours and concentrated under vacuum. Dissolved in EtOAc (5ml) and washed with saturated NaHCO₃ solution (1X5ml) and saturated NaCl solution (5ml). Dried over Na₂SO₄, filtered and concentrated under vacuum to yield intermediate 9f. Mass spec 1098.5 MH⁺.

Step g: cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(1,1-dimethylethyl)imidazole)-Gly]

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Intermediate 9f (crude, 0.085mmol) was dissolved in Tfa (9.4ml) containing $i\text{Pr}_3\text{SiH}$ and H_2O (0.5ml), stirred for about 20 minutes and concentrated under vacuum. The crude mixture was purified by preparative HPLC on a C_{18} column using a gradient of 30% to 60% CH_3CN / 0.1 % Tfa over about 50 minutes. A second pass using a gradient of 32% to 80% CH_3CN / 0.2 % NH_4OAc over about 50 minutes was required to obtain good separation. Pure fractions were combined, concentrated, and lyophilized (2X10ml 0.5% HCl, then 1X10ml H_2O) to yield the title compound of Example 9, 9mg (10%). Mass spec. 998.4 MH⁺.

Example 10

10 cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly]

Example 10 was prepared according to scheme 1 in a manner analogous to Example 3 except that Fmoc-Phe-OSu was used in place of Fmoc-Trp-F in step d. Mass spec. 894.4 MH⁺

Example 11

15 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly]

Example 11 was prepared according to scheme 1 in a manner analogous to Example 3 except that Fmoc-Phe-OH was used in place of Fmoc-Trp-F and Fmoc-Tyr(OBzl)-OH was used in place of Fmoc-Val-F in step d. The Fmoc-Tyr(OBzl)-OH was activated with DCC and commercially available HOAt. The crude mixture in step g was composed of completely deprotected material (both Cbz and benzyl ether removed) and partially deprotected material (Cbz removed and benzyl ether intact). The less polar peak resulting from partial deprotection yielded the title compound of Example 11. Mass spec 1048.5 MH⁺.

Example 12

25 cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly]

Example 12 was prepared according to scheme 1 in a manner analogous to Example 3 except that Fmoc-Phe-OH was used in place of Fmoc-Trp-F and Fmoc-Tyr(OBzl)-OH was used in place of Fmoc-Val-F in step d. The Fmoc-Tyr(OBzl)-OH was activated with DCC and commercially available HOAt. The crude mixture in step g was composed of completely deprotected material (both Cbz and benzyl ether removed) and partially deprotected material (Cbz removed and benzyl ether intact).

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The more polar peak resulting from complete deprotection yielded the title compound of Example 12. Mass spec 958.4 MH⁺.

Example 13

cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly]

Example 13 was prepared according to scheme 1 in a manner analogous to Example 4 except that intermediate 11f, cyclo[Phe-D-Trp-Lys(Cbz)-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly] was used in place of intermediate 3f in step g. Mass spec 944.6 MH⁺.

Example 14

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly]

Example 14 was prepared according to Scheme 2 in a manner substantially analogous to Example 9 with the following differences:

Step h: 2-(1-(S)-((Fmoc-Trp-D-Trp-Lys(Cbz)-Tyr(Bzl))-amino)-2-phenylethyl)-4-(3-methoxyphenyl)-1-(triphenylmethyl)-imidazole

Peptide synthesis was performed in a manner analogous to step 9h except Fmoc-Trp-OSu was used in place of Fmoc-Phe-OSu, Fmoc-Lys(Boc)-OSu was used in place of Fmoc-Lys(Cbz)-OSu and Fmoc-Tyr(Bzl)-OSu was used in place of Fmoc-Val-OSu. Yield = 783mg (57%), Mass spec = 1370.6 MH⁺.

Step e: 1-((2-Ethoxy-2-oxoethyl)-2-(1-(S)-((Fmoc-Trp-D-Trp-Lys(Boc)-Tyr(OBzl))-amino)-2-phenylethyl)-4-(3-methoxyphenyl)-imidazole

Alkylation of intermediate 14h was accomplished in a manner similar to reaction 9h, yield = 640mg (80%), mass spec = 1456.3 MH⁺.

Step f: cyclo [Trp-D-Trp-Lys(Boc)-Tyr(Bzl)-Phe Ψ (4-(3-Methoxyphenyl)imidazole)-Gly]

Intermediate 14e (640mg, 0.44mmol) was dissolved in 15ml methanol and 2.5N NaOH (1ml, 2.5mmol) was added. The mixture was stirred for about ½ hour and then the pH was adjusted to about 7.0 by addition of 5% HCl solution. The methanol was removed under reduced pressure and the aqueous layer decanted. The residue was thoroughly dried under reduced pressure then dissolved in 15ml DMF. DCC (206mg, 1.0mmol) and HOBt (153mg, 1.0mmol) were added and the reaction allowed to stir overnight. The reaction was concentrated under vacuum, dissolved in EtOAc (10ml) and washed twice with 10% phosphate buffer, pH=5.5.

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The EtOAc layer was then applied to a silica gel column and the product eluted with more EtOAc. Product fractions were combined and concentrated to 240mg (46%) of intermediate 14f.

Step g: cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

5 Intermediate 14f (240mg, 0.20mmol) was dissolved in CH₂Cl₂ (10ml) and Tfa (10ml) containing iPr₃SiH (205ul, 1.0mmol) was added. The mixture was stirred at room temperature for about 15 minutes. The CH₂Cl₂ was evaporated under reduced pressure and the crude product was precipitated by addition of ether. Solvents were decanted and the residue was further purified by preparative HPLC on a C₁₈ column
10 using a gradient of 30% to 50% CH₃CN/ 0.1 % Tfa over about 55 minutes. Pure fractions were combined, concentrated and lyophilized (2X10ml 0.5% HCl, then 1X10ml H₂O) to yield the title compound of Example 14, 25mg (11%). Mass spec. 1087.4 MH⁺.

Example 15

15 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

Example 15 was prepared according to synthetic scheme 1 in a manner substantially analogous to Example 4 with the following exception:

Step g: cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

20 Intermediate 1f (130mg, 0.115mmol) was dissolved in CH₂Cl₂ (5ml) and a solution of 1M BBr₃ in hexanes (5ml) was added under N₂. The resulting slurry was stirred for about ½ hour then cooled to about 0°C. Methanol (10ml) was added and the mixture was concentrated under vacuum. The crude mixture was applied to a C₁₈ column, washed with 1% NH₄OAc solution, washed with 0.1% Tfa solution and then eluted using a gradient of 20% to 35% CH₃CN/ 0.1% Tfa over about 50 minutes.
25 Pure fractions were combined, concentrated, and lyophilized (2X10ml 0.5% HCl) to yield the title compound of Example 15, 60mg (54%). Mass spec. 896 MH⁺.

Example 16

cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

30 Example 16 was prepared according to scheme 1 in a manner substantially analogous to Example 3 with the following differences:

Step d: 2-(1-(S)-((Fmoc-Phe-D-Trp-Lys(Cbz)-Nal)-amino)-2-phenylethyl)-4-(3-methoxyphenyl)-1-(triphenylmethyl)-imidazole

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Intermediate 16d was prepared in a manner substantially similar to intermediate 1d except that Fmoc-Nal-OAt was used in place of Fmoc-Val-F and Fmoc-Phe-OH was used in place of Fmoc-Tyr(Bzl)-OH.

Step g: cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly]

5 Step 16g was carried out in a manner substantially analogous to step 4g to yield the title compound of Example 16. Mass spec

Example 17

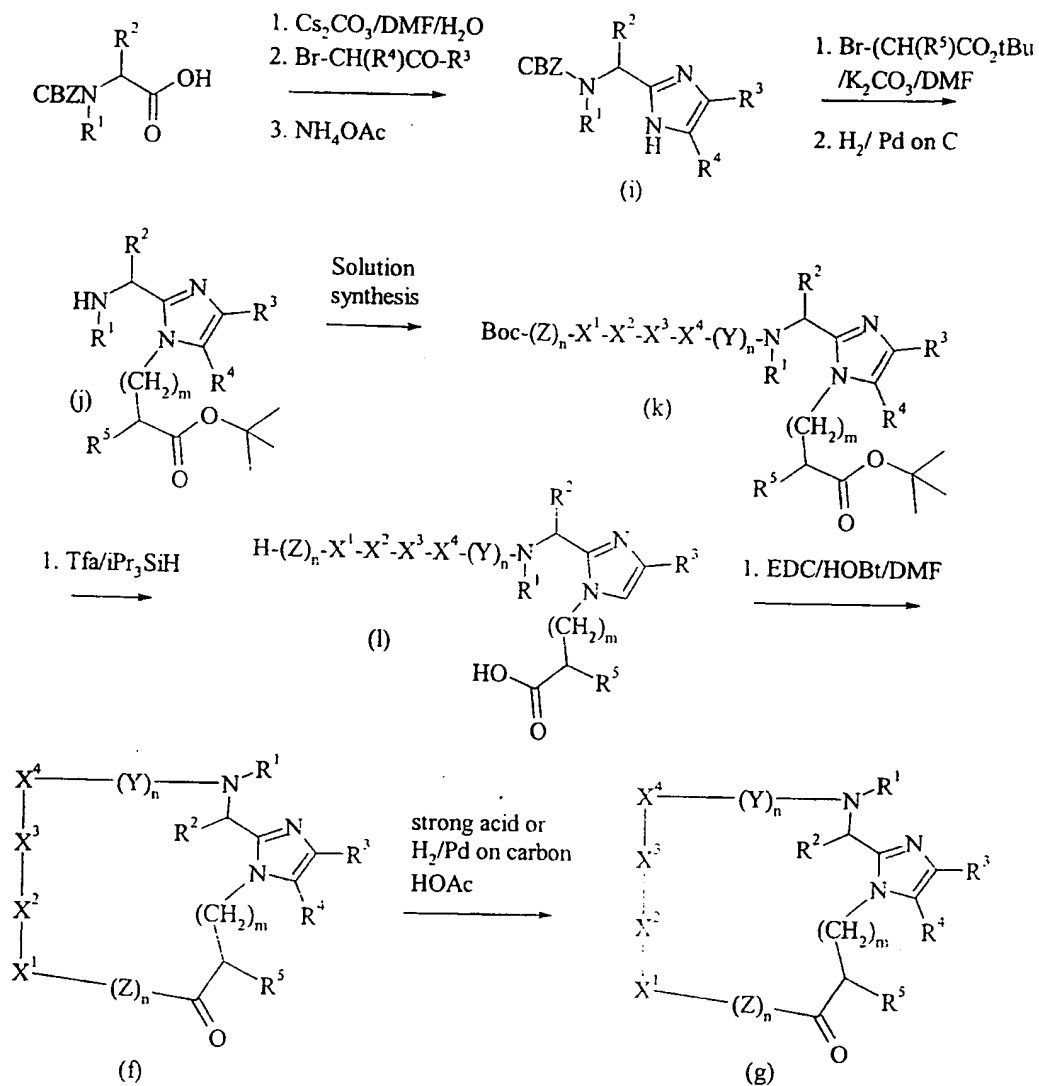
cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

10 Example 17 was prepared according to scheme 1 in a manner substantially analogous to Example 16 with the following exceptions:

Step g: cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly]

15 Intermediate 17f (310mg, 0.27mmol) was suspended in anisole (3ml) and the suspension was treated with about 12ml anhydrous HF. The mixture was stirred for about 1 hour at about 0°C. The HF was distilled off and the product precipitated by addition of ether. The crude product was filtered off and further purified by preparative HPLC using a gradient of 20-80% CH₃CN / 0.1% Tfa over about 40 minutes. Pure fractions were combined, concentrated and lyophilized twice from dilute HCl solution. Yield = 56mg (19%), Mass spec. 992.4 MH⁺.

SCHEME 3



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Example 18

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu]

5 Example 18 was prepared according to synthetic scheme 3.

Step i: 2-(1-(S)-((Phenylmethoxy)carbonyl)-amino-2-phenylethyl)-4-(4-methoxyphenyl)-imidazole

 Cbz-(L)-Phenylalanine (10.0g, 33.4mmol) and Cs₂CO₃ (5.44g, 16.7mmol) were combined in 2:1 / DMF:H₂O (75 ml) and the mixture was swirled until
10 homogeneous. Solvents were removed under reduced pressure, the residue was dissolved in DMF (70ml) and 2-bromo-3'-methoxyacetophenone (7.65g, 33.4mmol) in DMF (30ml) was added. The mixture was stirred for about ½ hour at room temperature then concentrated under reduced pressure. The resulting keto-ester was dissolved in xylenes (150ml) and the CsBr was filtered off. Ammonium acetate
15 (40.0g, 0.52 mol) was added and the mixture was heated at reflux for about 2 hours with removal of excess NH₄OAc and liberated H₂O using a Dean-Stark trap. The reaction was cooled and washed with saturated NaHCO₃ solution (50ml) and saturated NaCl solution (50ml). The xylenes layer was dried over Na₂SO₄, filtered and concentrated under vacuum to yield intermediate 18i as a tan solid (13.8g,
20 96%). Mass spec. 428.2 (MH⁺).

Step j: 2-(1-(S)-amino-2-phenylethyl)-1-(4-(1,1-dimethylethoxy)-4-oxo-butyl)-4-(4-methoxyphenyl)-imidazole

 Intermediate 18i (2.14g, 5.0mmol) was dissolved in DMF (11.5ml) and treated with KHCO₃ (1.50g, 15.0mmol) and 4-bromo-t-butylbutyrate (6.69g, 30mmol) in three
25 portions with stirring at about 50°C for about 18 hours. The mixture was diluted with ether and washed once with saturated NaHCO₃ solution and once with saturated NaCl solution. The ether layer was dried over Na₂SO₄, filtered and concentrated to an oil. Column chromatography on silica gel using CH₂Cl₂ as eluant yielded product as an oil.

30 The crude alkylated product was deprotected by hydrogenation in acetic acid using 10% Pd on carbon as catalyst. The catalyst was filtered off and solvents evaporated under reduced pressure. The residue was dissolved in EtOAc and

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washed with saturated NaHCO_3 solution and saturated NaCl solution, dried over Na_2SO_4 and concentrated to yield intermediate 18j as an oil (450mg) which was used in the next step without further purification.

Step k: 2-(1-(S)-((Boc-Trp-D-Trp-Lys(Cbz)-Val)-amino-2-phenylethyl)-1-((4-(1,1-dimethylethoxy)-4-oxo)butyl)-4-(3-methoxyphenyl)-imidazole

The solution synthesis was performed in a manner analogous to the synthesis detailed in step 1d except that Boc-Trp-OSu was used in place of Fmoc-Tyr(OBzl)-OSu and Fmoc-Tyr(OBzl)-OAt was used in place of Fmoc-Val-F to yield intermediate 18k. Yield = 1.03g (81%).

Step l: 2-(1-(S)-((H-Trp-D-Trp-Lys(Cbz)-Val)-amino-2-phenylethyl)-1-((4-hydroxy-4-oxo)butyl)-4-(3-methoxyphenyl)-imidazole

Intermediate 18k was treated with a solution containing $(i\text{Pr})_3\text{SiH}$ (593ul, 2.90mmol) in Tfa (10ml) and stirred for about one hour. The reaction was concentrated and triturated with 1:1 ether:hexanes solution to yield intermediate 18l as a tan solid which was used in the next step without further purification. Mass spec. 1267.7 MH^+

Step f: cyclo [Trp-D-Trp-Lys(Cbz)-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu]

Intermediate 18l was dissolved in DMF (20ml) and 4-methylmorpholine (159ul, 1.45mmol), HOBt (196mg, 1.45mmol) and EDC (278mg, 1.45mmol) were added and the reaction was stirred overnight. The reaction was concentrated under vacuum and purified by flash chromatography on silica gel using CH_2Cl_2 :MeOH (9:1) as eluant to yield intermediate 18f. Yield = 220mg (24%). Mass spec. 1249.7 MH^+

Step g: cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu]

Intermediate 18f (220mg, 176umol) was partially hydrogenated in acetic acid under 30psi of H_2 at room temperature using 10% Pd on C as catalyst for about 14 hours. The catalyst was filtered off and the filtrate concentrated under vacuum. The crude mixture was purified by preparative HPLC on a C_{18} column using a gradient of 0% to 75% CH_3CN / 0.1 % Tfa over 40 minutes. Pure fractions of the product peak were combined, concentrated, and lyophilized (2X10ml 0.5% HCl, then 1X10ml H_2O) to yield the title compound of Example 18, 72mg (37%). Mass spec. 1115.6 MH^+ .

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Example 19

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly]

Example 19 was prepared according to Scheme 3 in a manner substantially similar to Example 18 with the following differences:

- 5 Step j: 2-(1-(S)-amino-2-phenylethyl)-1-(2-(1,1-dimethylethoxy)-2-oxo-ethyl)-4-(4-methoxyphenyl)-imidazole

Intermediate 18i (854mg, 2.0mmol) was dissolved in DMF (10ml) and *tert*-Butyl bromoacetate (646ul, 4.0mmol) and K₂CO₃ (552mg, 4.0mmol) were added and the reaction was stirred at room temperature overnight. Solvents were removed
10 under reduced pressure and the residue dissolved in EtOAc and washed with saturated NaCl solution. The EtOAc layer was dried over Na₂SO₄, filtered and concentrated under vacuum to yield 1.02g foam. Mass spec. 428.2 MH⁺, NMR (300MHz, DMSO-d₆), 7.85-8.0 (1H,d), 7.6-7.75 (2H,d), 7.85-7.95 (1H,s), 7.1-7.35 (10H,m), 6.9-7.0 (2H,d), 4.75-5.05 (5H,m), 3.7-3.9 (3H,s), 3.1-3.4 (2H,m), 1.3-1.5
15 (9H,s).

The intermediate white foam (1.02g, 1.88mmol) was dissolved in HOAc (50ml) containing 10% Pd on C (50mg) and hydrogenated at room temperature under 30psi of H₂ for 10 hours. Catalyst was filtered off and 2N HCl (940uL, 1.88mmol) was added. The mixture was lyophilized once and then re-lyophilized
20 from 20% CH₃CN/H₂O to yield intermediate 19j as a light brown solid (862mg,) which was used without further purification. Mass spec. 408.2 MH⁺.

Step g: Catalytic hydrogenation and work-up performed in a manner substantially analogous to step 18g yielded the title product (22mg, 4%) as a white solid. Mass spec. 1088.2 MH⁺.

25

Example 20

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly]

Example 20 was prepared according to Scheme 3 in a manner substantially analogous to Example 18 except that 2-bromoacetophenone was used in place of 2-bromo-3'-methoxyacetophenone in step i. Mass spec. 1057.4 MH⁺

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Example 21

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(ε)Ahx]

Example 21 was prepared according to Scheme 3 in a manner substantially analogous to Example 18 with the following differences:

- 5 Step j: 2-(1-(S)-Amino-2-phenylethyl)-1-(6-(ethoxy)-6-oxo-hexyl)-4-(3-methoxyphenyl)-imidazole

Intermediate 21i (855mg, 2.0mmol) was dissolved in DMF (8.0ml) and treated with KHCO₃ (200mg, 2.0mmol) and ethyl 6-bromohexanoate (3.56ml, 20mmol) at about 120°C for about 8 hours. The mixture was concentrated and the residue was
10 purified by column chromatography on silica gel using 2:1/hexanes:EtOAc as eluant to yield pure product as a gum (0.94g).

The crude alkylated product was deprotected by hydrogenation in acetic acid using 10% Pd on carbon as catalyst. The catalyst was filtered off and solvents evaporated under reduced pressure. The residue was dissolved in dilute HCl, frozen
15 and lyophilized to yield intermediate 21j as a pale yellow solid, (720mg, 91%) which was used in the next step without further purification. Mass spec. 436.2 MH+

Step k and step l: 2-(1-(S)-((H-Trp-D-Trp-Lys(Boc)-Tyr(OBzl)- 2-(1-(S)-amino-2-phenylethyl)-1-(6-(ethoxy)-6-oxo-hexyl)-4-(3-methoxyphenyl)-imidazole

Fmoc-Tyr(OBzl)-OAt was prepared by mixing Fmoc-Tyr(OBzl)-OH (493mg,
20 1.00 mmol), HOAt (136mg, 1.0mmol) and DCC (206mg, 1.0mmol) in 8 ml EtOAc for about ½ hour then filtering off the dicyclohexylurea. The resulting solution was added to a solution of intermediate 21j (457mg, 0.9mmole) in EtOAc (4ml) and the mixture was stirred over saturated NaHCO₃ solution (10ml) until the reaction was complete by mass spectral analysis. The aqueous layer was removed and the
25 EtOAc layer was dried over Na₂SO₄, filtered and treated with tris(2-aminoethyl)amine (2.7ml). The mixture was stirred vigorously for about ½ hour. The EtOAc layer was washed with saturated NaCl solution (2 X 60ml) and then with 10% phosphate buffer the solution was adjusted to about pH=5.5 (3 X 15ml).

The intermediate was sequentially deprotected and coupled with Fmoc-
30 Lys(Cbz)-OSu, Fmoc-D-Trp-OSu and Fmoc-Trp-OSu in a manner substantially similar to the Fmoc-Tyr(OBzl)-OAt cycle described immediately above. A final Fmoc deprotection yielded the N-terminally deprotected intermediate ethyl ester. The

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EtOAc layer was dried over Na_2SO_4 , filtered and diluted with 4 volumes of hexanes. Solvents were poured off and the residue was triturated with hexanes to yield product as a solid (0.67g, 58%) which was used without further purification. Mass spec. 1289.6 MH⁺.

5 The ethyl ester was removed by treatment of intermediate in MeOH (5.0ml) with 1.7M NaOH solution (1.7ml) overnight. The mixture was adjusted to about pH=8.2 with 5% HCl solution and the solvents were removed under reduced pressure. The residue was taken up in DMF, the NaCl was removed by filtration and the DMF solution was taken to the next step without further purification.

10 Cyclization and deprotection were carried out in a manner analogous to Example 18 to yield the title compound of Example 21 as a white powder, 62mg. Mass spec. 1143.9 MH⁺

Example 22

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-hydroxyphenyl)imidazole-(γ)Abu]

15 Example 22 was prepared according to Scheme 3 in a manner substantially analogous to Example 18 with the following differences:

step j: 2-(1-(S)-Amino-2-phenylethyl)-1-(4-(ethoxy)-4-oxo-butyl)-4-(4-hydroxyphenyl)-imidazole

Intermediate 22i (2.0g, 4.68mmol) was dissolved in DMF (7.0ml) and treated
20 with KHCO_3 (468mg, 4.68mmol) and ethyl 4-bromo-butyrate (6.70ml, 46.8mmol) and stirred at about 100°C for about 30 hours. The mixture was diluted with ether and washed once with saturated NaHCO_3 solution and once with saturated NaCl solution. The ether layer was dried over Na_2SO_4 , filtered and concentrated to an oil. Column chromatography on silica gel using CH_2Cl_2 as eluant yielded product as an oil (2.53g,
25 94%). Mass spec. 542.3 MH⁺

The crude alkylated product (2.53g, 4.67mmol) in CH_2Cl_2 (50ml) was added dropwise over about 15 minutes at about -10°C to a solution of 1M BBr_3 /hexanes (23.4ml) in CH_2Cl_2 (250ml). The mixture was allowed to warm to room temperature and stirred for about 2 hours. Ethanol (40ml) was added and the mixture was
30 concentrated to about 50ml. The solution was diluted with ethanol (100ml) and allowed to stir overnight at room temperature. The mixture was concentrated under reduced pressure and the residue was distributed between EtOAc and saturated

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NaHCO₃ solution. The EtOAc layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to an oil (1.41g, 76%), which was used in subsequent steps without protection of the phenol. Mass spec. 394.3 MH⁺

HPLC Retention Times

Example No.	HPLC system	Retention time (minutes)
1	A	13.65
2	A	18.50
3	A	16.03
4	B	6.97
5	C	20.41
6	C	11.75
7	D	9.53
8	B	11.02
9	E	7.69
10	J	6.02
11	F	4.18
12	G	4.11
13	H	5.50
14	G	6.16
15	I	17.03
16	K	9.12
17	J	8.11
18	J	8.86
19	L	6.47
20	M	6.65
21	G	8.14
22	N	12.10

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HPLC systems:

- 5 A: Gradient: 20-80% CH₃CN / 0.1% Tfa, 24min.
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18
- 10 B: Gradient: 35-50% CH₃CN / 0.1% Tfa, 24min.
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18
- 15 C: Gradient: 32-64% CH₃CN / 0.1% NH₄OAc, 24min.
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18
- 20 D: Gradient: 20-60% CH₃CN / 0.1% Tfa, 24min.
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18
- 25 E: Gradient: 55-75% CH₃CN / 0.1% Tfa, 24min.
 Flow rate: 1.0 ml / min.
 Detection: 220nm
 Column: Phenomenex LICHROSPHERE® 5 RP18 (Phenomenex, 2320
 W
 205th St., Torrance, CA)
- 30 F: Gradient: 60% CH₃CN / 0.1% Tfa, isocratic
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18
- G: Gradient: 50% CH₃CN / 0.1% Tfa, isocratic
 Flow rate: 1.0 ml / min.
 Detection: 254nm
 Column: VYDAC® Protein and Peptide C18

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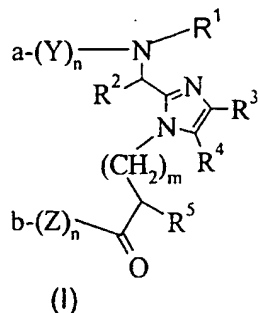
- H: Gradient: 38% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min.
Detection: 254nm
Column: VYDAC® Protein and Peptide C18
- 5 I: Gradient: 20-40% CH₃CN / 0.1% Tfa, 24min.
Flow rate: 1.0 ml / min.
Detection: 254nm
Column: VYDAC® Protein and Peptide C18
- 10 J: Gradient: 50% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min.
Detection: 254nm
Column: NUCLEOSIL™ C18, 5micron (Alltech Associates, 2051
Waukegan Rd., Deerfield, Illinois)
- 15 K: Gradient: 40% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min.
Detection: 254nm
Column: NUCLEOSIL™ C18, 5micron
- 20 L: Gradient: 52% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min.
Detection: 254nm
Column: NUCLEOSIL™ C18, 5micron
- 25 M: Gradient: 50% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min
Detection: 254nm
Column: NUCLEOSIL™ C18, 5micron
- N: Gradient: 48% CH₃CN / 0.1% Tfa, isocratic
Flow rate: 1.0 ml / min
Detection: 254nm
Column: NUCLEOSIL™ C18, 5 micron

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CLAIMS

What is claimed is:

1. A compound of the formula (I),



- 5 or a pharmaceutically acceptable salt thereof,
wherein,
Y and Z for each occurrence are each independently a D- or L-natural or unnatural
 α -amino acid;
n for each occurrence is independently 0 to 50, provided that both n cannot be 0 at
10 the same time;
m is 0 or an integer from 1 to 10;
a is H or R¹;
b is OH, -OR¹ or -NR⁹R⁹;
or a is taken together with b to form an amide bond;
15 R¹ is independently H, (C₁-C₄)alkyl or aryl-(C₁-C₄)alkyl;
R² is H or an optionally substituted moiety selected from the group consisting of (C₁-
C₄)alkyl, phenyl, phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the
optionally substituted moiety is optionally substituted by one or more substituents
each independently selected from the group consisting of (C₁-C₄)alkyl, (C₃-
20 C₈)cycloalkyl, -O-R⁶, -S(O)_q-R⁷,
-N(R⁹R⁹), -NHCO-R⁶, -NHSO₂R⁹, -CO₂R⁹, -CONR⁹R⁹ and -SO₂NR⁹R⁹, where q is 0,
1, 2 or 3;
R³ and R⁴ are each independently H, halo or an optionally substituted moiety
selected from the group consisting of (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl and aryl-
25 (C₁-C₄)alkyl; where the optionally substituted moiety is optionally substituted by one

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or more substituents selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo; or R³ and R⁴ are taken together with the carbons to which they are attached to form optionally substituted aryl, where the aryl is optionally substituted by one or more substituents each independently selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOR⁵, -CONR⁹R⁹ and halo;

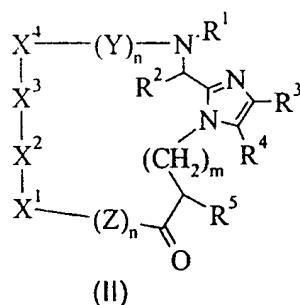
R⁵ for each occurrence is independently H, or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl and aryl-(C₁-C₄)alkyl, where the optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, OH, (C₁-C₄)alkoxy, aryloxy, NO₂, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;

R⁶ for each occurrence is independently selected from the group consisting of H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryl-(C₁-C₄)alkyl and aryl-(C₁-C₄)alkoxy;

R⁷ is H when q is 3 or, R⁷ for each occurrence is independently selected from the group consisting of (C₁-C₄)alkyl, aryl or aryl-(C₁-C₄)alkyl when q is 0, 1 or 2; and

R⁹ for each occurrence is independently selected from the group consisting of H, NO₂, (C₁-C₄)alkyl, aryl and aryl-(C₁-C₄)alkyl.

2. A compound of the formula (II),



or a pharmaceutically acceptable salt thereof,

wherein,

Y and Z for each occurrence are each independently a D- or L-natural or unnatural α-amino acid;

m is 0 or an integer from 1 to 10;

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n for each occurrence is independently 0 to 6;

R¹ for each occurrence is independently H, (C₁-C₄)alkyl or aryl-(C₁-C₄)alkyl;

R² is H or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl, phenyl, phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the

- 5 optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, cycloalkyl, -O-R⁶,

-S(O)_q-R⁷, -N(R⁹R⁹), -NHCO-R⁶, -NHSO₂R⁹, -CO₂R⁹, -CONR⁹R⁹ and -SO₂NR⁹R⁹,

where q is 0, 1, 2 or 3;

- 10 R³ and R⁴ are each independently H, halo or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl, cycloalkyl, aryl and aryl-(C₁-C₄)alkyl; where the optionally substituted moiety is optionally substituted by one or more substituents selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;
- 15 or R³ and R⁴ are taken together with the carbons to which they are attached to form optionally substituted aryl, where the aryl is optionally substituted by one or more substituents each independently selected from the group consisting of OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryloxy, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOR⁵, -CONR⁹R⁹ and halo;

- 20 R⁵ for each occurrence is independently H, or an optionally substituted moiety selected from the group consisting of (C₁-C₄)alkyl and aryl-(C₁-C₄)alkyl, where the optionally substituted moiety is optionally substituted by one or more substituents each independently selected from the group consisting of (C₁-C₄)alkyl, OH, (C₁-C₄)alkoxy, aryloxy, NO₂, aryl-(C₁-C₄)alkoxy, -NR⁹R⁹, COOH, -CONR⁹R⁹ and halo;

- 25 R⁶ for each occurrence is independently selected from the group consisting of H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, aryl-(C₁-C₄)alkyl and aryl-(C₁-C₄)alkoxy;

R⁷ is H when q is 3, or R⁷ for each occurrence is independently selected from the group consisting of (C₁-C₄)alkyl, aryl or aryl-(C₁-C₄)alkyl when q is 0, 1 or 2; and

- 30 R⁹ for each occurrence is independently selected from the group consisting of H, NO₂, (C₁-C₄)alkyl, aryl and aryl-(C₁-C₄)alkyl.

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X¹ is a natural or unnatural D- or L- α -amino acid, where when X¹ is Phe, Nal, Trp, Tyr, Pal or His the aromatic ring thereof is optionally substituted on carbon or nitrogen by R⁶ or when X¹ is Ser or Thr, the side chain oxygen is optionally substituted by one or more R¹;

5 X² is D- or L-Trp, N-methyl-D-Trp or N-methyl-L-Trp;

X³ is Lys, α -N-methyl-Lys or ϵ -N-(C₁-C₄)alkyl-Lys or ϵ -N-[aryl-(C₁-C₄)alkyl]-Lys;

X⁴ is a natural or unnatural D- or L- α -amino acid where when X⁴ is Phe, Nal, Trp, Tyr or His, the aromatic ring thereof is optionally substituted on carbon or nitrogen by R⁸ or when X⁴ is Ser, Tyr or Thr, the side chain oxygen may be substituted with one or
10 more R¹.

3. A compound according to claim 2, wherein

each n is 2;

m is 0 or 1 to 5;

R¹ for each occurrence is independently H, methyl or aryl-(C₁-C₄)alkyl;

15 R² is an optionally substituted moiety selected from the group consisting phenyl-(C₁-C₄)alkyl and heterocyclyl-(C₁-C₄)alkyl, where the optionally substituted moiety is substituted by a substituent selected from the group consisting of (C₁-C₄)alkyl and -O-R⁶; and

R³ and R⁴ are each independently H, halo or an optionally substituted moiety
20 selected from the group consisting of (C₁-C₄)alkyl and aryl; where the optionally substituted moiety is optionally substituted by a substituent selected from the group consisting of OH, (C₁-C₄)alkoxy, aryloxy and halo.

4. A compound according to claim 3, wherein

X¹ is Phe, Nal, Trp, Tyr, Pal or His, wherein the aromatic ring thereof is optionally
25 substituted on carbon or nitrogen by R⁶; and

X⁴ is Val, Abu, Ser, Thr, Nal, Trp, Tyr or His, wherein the aromatic ring of Nal, Trp, Tyr and His is optionally substituted on carbon and/or nitrogen by R⁸ or when X⁴ is Ser, Tyr or Thr, the side chain oxygen is optionally substituted by R¹.

5. A compound according to claim 4, wherein

30 X¹ is Phe, Trp or Tyr wherein the aromatic ring thereof is optionally substituted on carbon or nitrogen by R⁶;

X² is D-Trp or N-methyl-D-Trp;

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X³ is Lys or α -N-methyl-Lys;

X⁴ is Val, Thr, Abu, Nal or Tyr, wherein the side chain oxygen of the hydroxy group of Thr and Tyr is optionally substituted by R¹;

R¹ for each occurrence is independently H, methyl or benzyl;

- 5 R² is an optionally substituted moiety selected from the group consisting of phenylmethyl and heterocycliyl-methyl, where the optionally substituted moiety is substituted by a substituent selected from the group consisting of (C₁-C₄)alkyl and -O-R⁶;

- 10 R³ is (C₁-C₄)alkyl or optionally substituted aryl; where the optionally substituted aryl is substituted by a substituent selected from the group consisting of OH, (C₁-C₄)alkoxy, aryloxy, and halo;

R⁴ is H; and

R⁶ for each occurrence is independently selected from the group consisting of H and aryl-(C₁-C₄)alkoxy.

- 15 6. A compound according to claim 5, wherein

X¹ is Phe, Trp, Tyr or Tyr(OBzl);

X⁴ is Val, Thr, Abu, Nal, or Tyr, wherein the hydroxy group of Thr and Tyr is optionally substituted benzyl;

m is 0, 2 or 4;

- 20 R² is an optionally substituted moiety selected from the group consisting of phenylmethyl or 3-indolylmethyl where the optionally substituted moiety is optionally substituted by -O-R⁶; and

- 25 R³ is 1,1-dimethylethyl or optionally substituted aryl; where the optionally substituted aryl is optionally substituted by a moiety selected from the group consisting of OH, (C₁-C₄)alkoxy and halo.

7. A compound according to claim 6, wherein

R² is phenylmethyl;

R³ is 1,1-dimethylethyl or optionally substituted phenyl, where the optionally substituted phenyl is optionally substituted by OH or OCH₃; and

- 30 R⁶ for each occurrence is independently selected from the group consisting of H or benzylmethoxy.

8. A compound according to claim 1, wherein said compound is

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H-Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly-OH:

9. A compound according to claim 7, wherein said compound is
 - cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Tyr(OBzl)-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - 5 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - 10 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 - 15 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 - cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],
 - cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],
 - cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],
 - 20 cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly],
 - cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(phenyl)imidazole-Gly],
 - cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(ε)Ahx] or
 - cyclo [Trp-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-hydroxyphenyl)imidazole-(γ)Abu].

10. A compound according to claim 9, wherein said compound is
 - 25 cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Tyr(OBzl)-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],
 - 30 cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],
 - cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole)-Gly],

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cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly] or

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

5 11. A compound according to claim 10 wherein said compound is

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

10 cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly] or

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

12. A compound according to claim 11 wherein said compound is

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

15 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly] or

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly].

13. A compound according to claim 9 wherein said compound is

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

20 cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Thr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Abu-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

25 cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(1,1-dimethylethyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Tyr(OBzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Tyr-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

cyclo [Tyr-D-Trp-Lys-Val-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

30 cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly),

cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly),

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cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(ε)Ahx] or

5 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-hydroxyphenyl)imidazole-(γ)Abu].

14. A compound according to claim 13 wherein said compound is

cyclo [Trp-D-Trp-Lys-Thr-Phe Ψ (4-(3-hydroxyphenyl)imidazole)-Gly],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],

cyclo [Phe-D-Trp-Lys-Nal-Phe Ψ (4-(3-hydroxyphenyl)imidazole-Gly],

10 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly] or

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly].

15. A compound according to claim 14 wherein said compound is

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-Gly],

15 cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(3-methoxyphenyl)imidazole-(γ)Abu],

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(4-methoxyphenyl)imidazole-Gly] or

cyclo [Trp-D-Trp-Lys-Tyr(Bzl)-Phe Ψ (4-(phenyl)imidazole-Gly].

16. A pharmaceutical composition comprising an effective amount of a

compound according to claim 1 or a pharmaceutically acceptable salt thereof and a

20 pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising an effective amount of a

compound according to claim 2 or a pharmaceutically acceptable salt thereof and a

pharmaceutically acceptable carrier.

18. A method of eliciting a somatostatin receptor agonist effect in a

25 mammal in need thereof, which comprises administering to said mammal an

effective amount of a compound according to claim 1 or a pharmaceutically

acceptable salt thereof.

19. A method of eliciting a somatostatin receptor agonist effect in a

mammal in need thereof, which comprises administering to said mammal an

30 effective amount of a compound according to claim 2 or a pharmaceutically

acceptable salt thereof.

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20. A method of eliciting a somatostatin receptor antagonist effect in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

5 21. A method of eliciting a somatostatin receptor antagonist effect in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound according to claim 2 or a pharmaceutically acceptable salt thereof.

10 22. A method of treating prolactin secreting adenomas restenosis, diabetes mellitus, hyperlipidemia, insulin insensitivity, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon, Nephropathy; gastric acid secretion, peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery diarrhea syndrome, AIDS related diarrhea, chemotherapy-induced diarrhea, acute or chronic pancreatitis, gastrointestinal
15 hormone secreting tumors, cancer, hepatoma, angiogenesis, inflammatory disorders, arthritis, chronic allograft rejection, angioplasty, graft vessel bleeding or gastrointestinal bleeding, in a mammal in need thereof, which comprises administering to said mammal a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

20 23. A method of treating prolactin secreting adenomas restenosis, diabetes mellitus, hyperlipidemia, insulin insensitivity, Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon, Nephropathy; gastric acid secretion, peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery diarrhea syndrome, AIDS related diarrhea,
25 chemotherapy-induced diarrhea, acute or chronic pancreatitis, gastrointestinal hormone secreting tumors, cancer, hepatoma, angiogenesis, inflammatory disorders, arthritis, chronic allograft rejection, angioplasty, graft vessel bleeding or gastrointestinal bleeding, in a mammal in need thereof, which comprises administering to said mammal a compound according to claim 2 or a
30 pharmaceutically acceptable salt thereof.

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24. A method of inhibiting the proliferation of *helicobacter pylori* in a mammal in need thereof, which comprises administering to said mammal a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

25. A method of inhibiting the proliferation of *helicobacter pylori* in a
5 mammal in need thereof, which comprises administering to said mammal a compound according to claim 2 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/13304

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/655 C07D33/64 A61K31/4164 A61K38/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 30053 A (BIOMEASURE INC) 21 August 1997 (1997-08-21) See especially claims 1,3,29 and 30 ---	1, 16, 22
A	C.GILON E.A.: "A backbone-cyclic, receptor 5-selective somatostatin analogue: synthesis, bioactivity and NMR conformational analysis" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 5, 26 February 1998 (1998-02-26), pages 919-929, XP002119955 WASHINGTON US cited in the application the whole document --- -/--	1-25

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 October 1999

Date of mailing of the international search report

05/11/1999

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Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/13304

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SHIMON L ET AL: "SOMATOSTATIN RECEPTOR SUBTYPE SPECIFICITY IN HUMAN FETAL PITUITARY CULTURES"</p> <p>JOURNAL OF CLINICAL INVESTIGATION, vol. 99, no. 4, 15 February 1997 (1997-02-15), pages 789-798, XP002073099</p> <p>ISSN: 0021-9738</p> <p>cited in the application</p> <p>the whole document</p> <p style="text-align: center;">---</p>	1-25
A	<p>WO 98 04583 A (YISSUM RES DEV CO ;GILON CHAIM (IL); GELLERMAN GARY (IL); HORNIK V)</p> <p>5 February 1998 (1998-02-05)</p> <p>the whole document</p> <p style="text-align: center;">-----</p>	1-25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/13304

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730053 A	21-08-1997	AU 1964597 A	02-09-1997
		CA 2245823 A	21-08-1997
		CN 1216545 A	12-05-1999
		EP 0904274 A	31-03-1999
		PL 328513 A	01-02-1999
		ZA 9701254 A	14-07-1998
WO 9804583 A	05-02-1998	US 5770687 A	23-06-1998
		AU 3633197 A	20-02-1998
		EP 0920446 A	09-06-1999